Universidade de Aveiro
Ano 2016

Departamento de Ciências Médicas

Sónia Domingues Cipriano

Desenvolvimento Farmacêutico: desenvolvimento galénico de um medicamento genérico

Pharmaceutical Development : Galenical development of a generic drug product

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Projeto apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado da Universidade de Aveiro.

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agradecimentos

A Concretização de um Mestrado é um processo complexo e trabalhoso, que só se torna realizável com o apoio e o suporte de pessoas fundamentais, às quais gostaria de deixar o meu agradecimento.

Em primeiro lugar, agradeço ao Professor Doutor Bruno Gago não só pelos conhecimentos transmitidos nas aulas que tive o prazer de assistir, mas principalmente pela disponibilidade e simpatia com que sempre atendeu aos meus pedidos e dúvidas, revelando-se deste modo um grande apoio nestes anos decorrentes do Mestrado.

Agradeço ao Professor Doutor Luís Almeida pela inspiração, sentido de humor e ironia que sempre colocou nas temáticas abordadas nestes anos de Mestrado.

Agradeço à família Bluepharma, principalmente ao Dr. Gabriel Silva e à Doutora Sónia Alfar que me apoiaram e permitiram que disponibilizasse algum do meu tempo profissional para assistir a aulas e a exames.

Agradeço aos meus pais e à minha irmã que foram e sempre serão o meu principal suporte e porto de abrigo na vida, quer a nível pessoal, académico ou profissional.

Agradeço ainda ao meu marido, Ricardo Neta por todo o apoio, carinho e paciência que teve para comigo em todos os momentos deste percurso. Sem este apoio, não teria sido possível.

Palavras-chave

Desenvolvimento Farmacêutico, Desenvolvimento Galénico, Gestão de risco, Dossier de produto investigacional, Qualidade do produto, Formulação, Processo de Fabrico.

Resumo

O desenvolvimento de genéricos reveste-se de grande complexidade pela demanda de qualidade associada a qualquer produto farmacêutico acrescida da complexa interpretação de situação jurídica (patentes), da seleção de um vasto número de moléculas e tecnologias que trarão um claro custo-benefício e dos exigentes prazos para as colocar em mercados, muitas vezes com diferentes requisitos regulatórios.

Esta tese irá providenciar uma visão geral sobre um método standard numa indústria de desenvolvimento farmacêutico. O presente trabalho tem como objetivo descrever os pontos gerais de um desenvolvimento galénico, seguido por exemplos práticos, de forma a avaliar um projeto desde o seu estado conceptual até à fase de ensaio clínico.

De forma a dar uma visão clara de desenvolvimento galénico numa instalação de estado da arte, este trabalho irá abordar processos usados na análise da viabilidade de projetos, formulação, processos de fabrico e submissão de dossiers de produtos investigacionais.

Keywords Pharmaceutcal Development, Galenical Development, Risk Assessment, IMPD, Quality Target Product Profile, Critical Quality Attributes, Formulation, Manufacturing Process.

Abstract

The development of generics is a very complex area due to the demand for quality associated to any pharmaceutical product added to the complex interpretation of legal situation (patents), the selection of a large number of molecules and technologies that will bring a clear cost-benefit and the demanding deadlines for placing them in markets, often with different regulatory requirements.

This thesis will provide a general view of a standardized method used in a pharmaceutical development company. The present work intends to describe the general points of the galenical development followed by practical examples of this process, evaluating the project from its initial conceptual phase until clinical trial.

In order to portrait a clear picture of the galenical development on a state of the art facility, the work will access current processes used for project viability analysis, formulation, manufacturing processes and IMPD submission

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List of Abbreviations

ANDA – Abbreviated New Drug Application

API – Active Principle Ingredient

BCS – Biopharmaceutical Classification System

BE – Bioequivalent

BMR – Batch Manufacturing Record

BSE/TSE declaration - Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) declaration

CFT – Cross Functional Team

CQAs – Critical Quality Attribute

CU – Content Uniformity

CTDs – Common Technical Documents

Deg. Prod. – Degradation Products

DMF – Drug Master File

DP – Drug Product

DS – Drug substance

GMP – Good Manufacturing Practices

HDPE – High Density Polyethylene

HPMC – Hydroxypropyl Methyl Cellulose

IMP – Investigational Medicinal Product

IMPD – Investigational Medicinal Product Dossier

QTPP – Quality Target Product Profile

JP - Japanese

LOD – Loss on drying

MA – Marketing Authorization

MRA - Mutual Recognition Agreement

OGD – Office of Generic Drugs

Ph.Eur. – European Pharmacopeia

PK/PD – Pharmakocinetic/Pharmacodynamic

PSD – Particle Size Dimension

RLD – Reference Listed Drug

US – United States

USP – United States Pharmacopeia

1. Introduction

In order to accomplish my curricular plan for Master degree at University of Aveiro's Training Program in Pharmaceutical Medicine, my work focus on the development of a Project on Pharmaceutical development. More precisely about galenical development, area in which I presently work in Bluepharma.

This thesis will provide a general view of a standardized methods used in a pharmaceutical development company. This work intends to describe the general points of the galenical development followed by practical examples of this process, evaluating the project from its initial conceptual phase until clinical trial. The data of practical examples were obtained from pharmaceutical development reports, wherefore the confidentiality of the name of drug product or the drug substance were respected.

In order to portrait a clear picture of the galenical development on a state of the art facility, the work will access current processes used for project viability analysis, formulation, manufacturing processes and IMPD submission.

The data compiled during the elaboration of this thesis will allow Bluepharma to have a clear picture of the current pharmaceutical development. By accessing the existing strengths and weaknesses will yield a possible optimisation of the pharmaceutical development process.

1.1 Objectives

This thesis aims at describe the process of developing a project since it emerges as an idea until it is undergoes to clinical trial. Therefore, the issues covered by this thesis enclose the projects viability, a project management approach of the initial idea where it is decided if the project continues or not; a galenical development stage, where is briefly described the main critical points of formulation development; a scale-up and GMP production, where the collaborative work between galenical development and production have a crucial role in the success of the production of validation batches and finally a importance of the data generated by development department in the creation of the Investigational Medicinal Product Dossiers.

1.2 Project Structure

This report is divided in five sections. The Introduction, will briefly describe the objectives with the elaboration of this project work, as do the current state-of–the-art of formulation development and a short description of the host company. Project viability is described in section two, having as sub-topics the definition of markets, definition of timelines and milestones and economical viability of the project. Section three have a summarized approach to galenical development with themes as characterization of drug product (Active Substance and Excipients), manufacturing process, formulation development and optimization of galenical development processes. In section four, the elaboration of IMPDs is addressed as the documentation needed for the shipping of the investigational products. The accomplishment of the proposed objectives is discussed in final notes, on section five, the last section.

1.3 Pharmaceutical Development

The goal of pharmaceutical development activities is to design a quality product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients, healthcare professionals, regulatory authorities and internal customers' requirements. (ICH Q9, 2008)

The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space (multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality), specifications, and manufacturing controls.

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

The Pharmaceutical Development should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use.

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Inclusion of this additional information provides an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes and their controls. This scientific understanding facilitates establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk-based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- reduction of post-approval submissions; real-time quality control, leading to a reduction of end-product release testing. To realise this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters. (ICH Q8(R2), August 2009)

In Pharmaceutical Development, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge,

results of studies using design of experiments, use of quality risk management, and use of knowledge management throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application.

Pharmaceutical development should include, at a minimum, the following elements:

- Defining the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage form, bioavailability, strength, and stability;
- Identifying potential critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled;
- Determining the critical quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality;
- Selecting an appropriate manufacturing process;
- Defining a control strategy. (ICH Q8(R2), August 2009)

Development is divided into chemical and pharmaceutical development. The former covers the development of the active pharmaceutical ingredient (API). This is the ingredient which is responsible for a drug's therapeutic effect. Pharmaceutical development, on the other hand, deals with the development of the final drug product. Its administration form, e.g. a pill, a spray, or a liquid for injection, and dosage are essential for the therapeutic effect to unfold. (Ziegler, 2014)

The Pharmaceutical Development includes two major areas: the galenical development and the analytical development. The focus of this project is the galenical development approach with practical examples of one development done for a generic product in Bluepharma.

1.4 Host Company – Bluepharma

Bluepharma is a Portuguese capital pharmaceutical company, based in Coimbra. Bluepharma initiated its activity in February 2001, when a group of professionals, connected with the pharmaceutical industry, bought a state-of-the-art industrial unit from the German giant, Bayer.

Bluepharma concentrates its efforts on the manufacturing, development and marketing of pharmaceutical drugs. With over 30 years of experience in producing pharmaceutical products, they guarantee standards of the highest quality, based on the know-how of our technical staff, and vision and dynamism of our management team.

Bluepharma's activities are carried out in 3 distinct areas:

- Producing pharmaceutical drugs for Bluepharma and other companies;
- Research, development and registration of pharmaceutical drugs;
- Marketing of generic pharmaceuticals.

Bluepharma is committed to systematically ensuring the quality of manufactured and distributed medicinal products; to respecting the environment as well as safeguarding the working conditions of its employees. This is achieved through the implementation of a Quality, Environment, Health and Safety System, supported by ISO Norms 9001, ISO 14001 and OHSAS 18001, by the Good Manufacturing Practices and by other applicable legislation.

Their mission is to market pharmaceutical products of the highest quality at competitive prices, contributing for the rationalization of expenses in the health sector and simultaneously to the improvement of the life quality of populations. (Bluepharma Site)

2. Project Viability

At Bluepharma, before a project of development starts, a multidisciplinary group is formed to discuss the viability of the project (Evaluation Meetings). The team include one member of each department: galenical development, analytical development, business development, quality management, project management, production (manufacturing and packaging), regulatory affairs and production management. Each one expresses their technical opinion about the viability and feasibility of the project. The conclusions of that meetings are thereafter communicated to top management which decides if the project continues or not. The practical examples showed in the following sections (definition of markets, definition of timelines and economical viability) are a result of 3 fundamental Evaluation Meetings (project presentation, project discussion and final conclusion) which culminates in a final document/form of the analysis and classification of project idea.

This concept of integrated development approach contributes to a better communication and commitment of all the departments evolved in the success of the project.

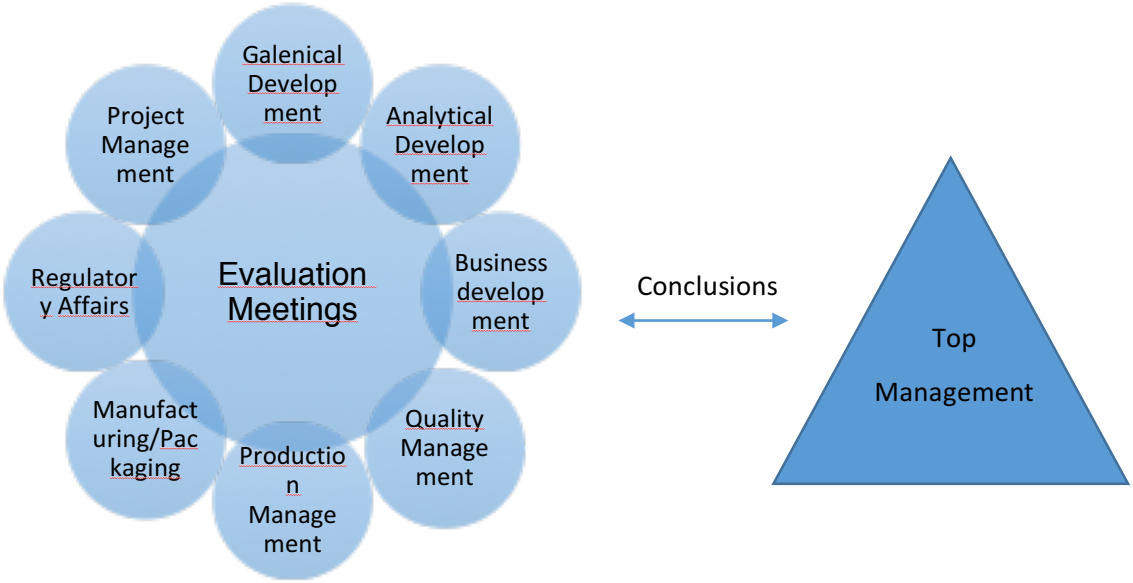

Figure 1 *– Relation between Evaluation Meetings, their intervenients and Top management*

In cross-functional teams (CFT) different specialists of different organizational units find together to commonly work on a development project. They share information and take decisions about product, process, and production together (Koufteros, 2005). This functional and organizational diversity speeds up product development and improves development performance (Koufteros, 2005). Mainly, it is ensured that production is involved in the development and developed manufacturing processes are viable. A common process understanding and unified visions are central to prevent different interpretations and to compensate differences (Gerwin, 2002)

Goals and visions define boundaries for the team to prevent it from constantly re-defining itself and its tasks. Team autonomy enables the team to take decisions on its own.

A general climate supporting cross-functional collaboration is needed. Furthermore, a climate of importance and urgency of the project leads to constructive pressure.

The ideal team mix must be chosen to combine many different skills. By this, different inputs can be processed in a most reasonable way. Functional diversity “helps project team members to understand the design process more quickly and fully from a variety of perspective, and thus it improves design process performance. Moreover, the increased information helps the team to catch downstream problems such as manufacturing difficulties or market mismatches before they happen, when these problems are generally smaller and easier to fix” (Brown, 1995).

Strong team leadership enables the team. Furthermore, it provides directions for the team members without hindering them to work freely. Top management support should be visible by commitment to the project and the team. Top management should mainly be helping in the case of problems, it should encourage the team and be “making things happen” (McDonough, 2000).

Commitment of all team members is crucial for project success because it leads to common efforts in a common direction. Each team member must be willing to contribute to the overall project success. (Ziegler, 2014)

2.1 Definition of Markets

The definition of the Market intended to require the Market Authorization for a specific drug product is essential to define the steps and the rules needed for guiding the Pharmaceutical Development. Despite of the efforts of having requirements and guidelines standard for different markets, some activities are not fully harmonized, leading for that reason to constraints during development.

As example, the following table represents some of the differences between the two major markets: European and US Market.

Table 1 *- Differences between European and American Market in Pharmaceutical Development*

	US Market	**EU Market**
Excipients Analysis	According to USP	According to Ph. Eur.
Excipients Quantities	According to Inactive Ingredient Database	No requirements
Drug Substance Analysis	According to USP	According to Ph. Eur.
Shape and colour of tablets	Similar to Reference Product	No requirements
Release and shelf-life specifications (assay and degradation products)	Same specification limits	Different specification limits
Release Dissolution Medium	According to OGD requirements	Dissolution Medium developed
Container Closure System	Presentations to be intended for commercialization (usually bottles)	Presentations to be intended for commercialization (usually blisters)
Packaging	At a minimum of 100.000 units	No special quantities required
Process Validation	Not required at the time of submission	Required
Design of Clinical Trial	According to OGD recommendations (usually fast and fed conditions)	No such requirements
Retention Samples for Clinical Trial	5 times the sample required for analysis	No such requirements

2.2 Definition of Timelines/Milestones

In the pharmaceutical industry, new substances are filed for patent protection very early in the R&D process, often during discovery and before the beginning of product development. Thus, longer development time results in a shorter patent protection period during which it can be sold exclusively before competitors or generics manufacturer can imitate it. Usually, sales decrease up to 80% after patent expiry, mainly due to substitution by cheaper generics (Basu, 2010) . As a result, today's new pharmaceutical products must generate more money in less available time. Additionally, there is increasing pressure on drug prices by governments. This calls for stable and efficient manufacturing processes right from commercial launch to avoid inefficient and thus excessive manufacturing costs.

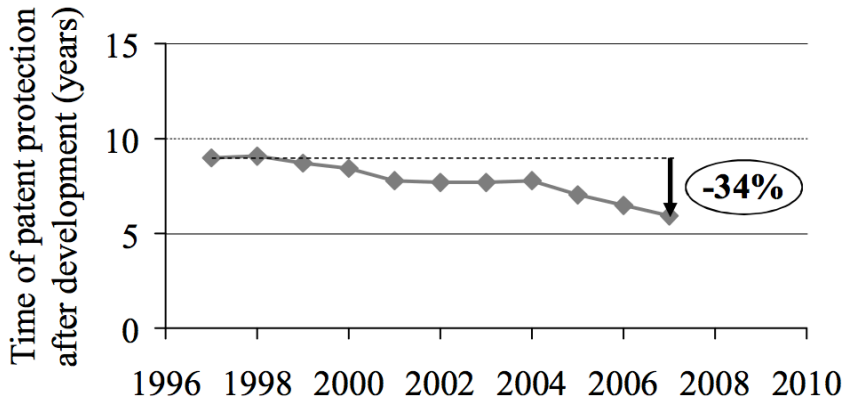

Figure 2 *- Time of patent protection after product launch (CMR International, 2008)*

During Evaluation meetings, the patent analysis is one of the topics addressed: is very important understand what type of patens are in force and what kind of protection their offer, e.g. use of the API, use of specific excipients or use of specific manufacturing process. According to this analysis is possible predict the difficulty level of the development. The expiry dates of the patents are also very important to estimate the time available to achieve the market.

A practical example of a patent analysis in the scope of Evaluation meetings is presented below. Note that the timelines defined does not correspond to reality, they were used only for showing the type of analysis made.

IP Landscape (Patent Analysis)

“There are no unexpired patents for this product in the Orange Book Data”. Exclusivity data: Nov 20, 2017.

As referred above the patent constraints have impact on the timelines of the project, but it is not the single factor. The supply of drug substance, excipients or packaging materials can also have an impact in the definition of timelines. A spot in industrial production or even the documentation preparation, such as BMRs (Batch Manufacturing Records), PVs (Validation Protocols) or later in the process, the submission of IMPDs (Investigational Medicinal Product Dossiers) or CTDs (Common Technical Document) are of great importance on the project management.

The clinical trial timelines are also a very important milestone in the scope of the project, as it can be seen below with the practical example:

Milestones of Clinical Trial

Table 2 *- Milestones of clinical trial*

Milestones	**Pilot Study (Study 1)**	**Pivotal Study (Study 2 and 3)***
IMPD ready	T0	T0
Ethics and	Week 1	Week 1
Study Approval	Week 5	Week 5
Site Ready	Week 6	Week 6
Screening	Week 6	Week 6
Period 1	Week 7	Week 7
Period 2	Week 8	Week 8
Samples Shipment	Week 8	Week 9
Bioanalytical Results	Week 11	Week 13
Clinical Study Report, Draft	Week 13	Week 15
Clinical Study Report, Final	5 days after Sponsor´s input	5 days after Sponsor´s input
*Considering that both studies will be conducted in parallel	~3.5 months	~4 months

General Milestones of the project

Table 3 *- General Timelines for the project*

Activity/Task	**Responsibility**	**Estimated Timelines**
Formulation Dev. – Part I	Galenical and Analytical Development	Dec-16
Pilot BE	Galenical and Analytical Development/ Medical Affairs	Apr-17
Formulation Dev. – Part II	Galenical and Analytical Development	May-17
Validation	Galenical and Analytical Development/ Production Management	Aug-17
ICH T=6M	Galenical and Analytical Development	Mar-18
BDBE	Galenical and Analytical Development/ Medical Affairs	Jan-18
Submission	Regulatory Affairs	Apr-18

2.3. Economical Viability of the Project

Despite of this topic are related to business development is important to refer that the study of the markets, including forecasts of sells, costs of APIs, prevision of costs with manufacturing and clinical trials are evaluated to know the economic viability of the project.

A practical example of an economic analysis of development for a generic product is expressed below. Note that the costs defined does not correspond to reality, they were used only for showing the type of analysis made.

Market Forecasts

Considering the lowest price currently marketed and the expected market share to achieve once this development comes to be a product on the market, it is expected an annual forecast of 7.500.000 tablets.

Sales and Consumption

The current USA market accounts for $82,4 million USD referring to a 12 months period ending in September 2016. Market intelligence considers that 80% ($65,92 million USD) of this market was overtaken by the generics once they became available in 2013.

Considering that this development will come to be the 3rd or 4th generic on the market it is expected that its sales will account for a range from $16.48 million USD to $21.97 million USD, considering the “fair share” approach.

The prices on the market in SEP 2016 are:

Table 4 - *Prices of Reference Product and generics in US market*

Product	Dosage	Pack	Price
Reference Product	0,1 mg	1 Tablet	3,07 USD
		60 Tablets	184,30 USD
Generic Product 1	0,1 mg	1 Tablet	3,02 USD
		60 Tablets	181,31 USD
Generic Product 2	0,1 mg	1 Tablet	2,20 USD
		60 Tablets	131,81 USD

Although there are registered pack sizes of 30's, 60's, 180's and 500's, data indicates that the only presentation on the market is the 60's. Following the innovator product strategy, the 60's pack is the focus of this development, however the 180's pack is not to be disregarded.

Competition

There are currently 3 players on the market, two generic drugs and the reference product. Both generic drugs were approved through an ANDA in 2013 and 2015 respectively. No other ANDA submissions are known for this product at present time.

Estimated budget for the project:

***Table 5** - Estimated budget for the project*

BDBE	RLD	API	Project Total Cost
50.000€ - Pilot	10.000€	2.000€	approx.. 300.000€
200.000€ - Pivotal			

Financial Projections:

In this topic, the company evaluates different scenarios of financial projections: best, base and worst scenario. This analysis states the viability of the project for each case.

3. Galenical Development Stage

3.1. Quality Target Product Profile (QTTP)

As discussed before, the quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs.

Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

Risk assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. (ICH Q8(R2), August 2009)

The following table show an example of a QTPP done in the initial stage on the Pharmaceutical development of a generic drug:

Table 6 *- Target Product Profile*

Attribute	Target Product Profile	Rationale
Dosage Form	Enteric Film-coated tablets (bilayer)	Pharmaceutical equivalence requirement: same dosage form. For identification, use an embossed tablet. Tablet Shape and Size to facilitate swallowing acc.to Guidance for Size, Shape, and Other Physical Attributes of Generic Tablets and Tablets
Route of administration	Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage Strength	12.5-mg yellow tablets, engraved with X 12.5 25-mg pink tablets, engraved with X 25 37.5-mg blue tablets, engraved with X 37.5.	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics	DS has a complete absorption after oral dosing; the elimination half-life is approximately 15 to 20 hours after a single dose of Reference Product X. DS extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. DS metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces	Bioequivalence requirement. Initial plasma concentration through the first two hours that provides a clinically significant therapeutic effect followed by a sustained plasma concentration that maintains the therapeutic effect Bioequivalence requirement – RLD defined to be used as Reference: Name of reference Product
Stability	At least 24 months of shelf-life Stored at or below 25ºC (77°F), in the bottle tightly closed.	Equivalent to or better than RLD shelf-life
Container closure system	HDPE Bottles of 30 and 100 counts – 12.5mg and 25mg HDPE Bottles of 30 counts – 37.5 mg	Needed to achieve the target shelf-life and to ensure tablet integrity during shipment.
Administration/ Concurrence with labeling	The tablet is to be taken as single daily dose and can be taken with or without food. Similar food effect as RLD	RLD = Name of reference Product (USA)
Alternative methods of administration	None	None are listed in the RLD labeling

Table 7 - *Definition of CQAs*

Quality Attributes of the Drug Product		Target Product Profile	Is this a CQA ?	Rationale
Physical Attributes	Appearance	Film coated, double layer, round and biconvex tablet. Color and aspect acceptable to the patient. No visual surface defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability. Pharmaceutical equivalence requirements: same dosage form.
	Odor	Have no unpleasant odor	No	Generally, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability and lead to complaints. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing.
	Size	Round 7mm diameter/ Round 8mm diameter	Yes	Tablet size correlates to swallowability; therefore, it is critical. For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet size and volume is set similar to the RLD. Equivalent to RLD, size defined by dosage.
	Tablet Identification	Tablet with a suitable color combination and embossing	Yes	Identification of the correct product being produced avoiding cross contamination.
Identification		Positive for drug substance	No	Formulation and Manufacturing Process are unlikely to impact identity.
Assay		100.0%±10% of label claim (for US)	Yes	Variability in assay will affect safety and efficacy; therefore, assay is critical. Formulation and Manufacturing Process may affect Uniformity. Pharmaceutical equivalence requirements: meet the same or better compendial quality standard of product.
Content Uniformity		Conforms to USP <905> Uniformity of Dosage Units 100% (AV < 15)	Yes	Variability in content uniformity will affect safety and efficacy. Content uniformity of tablets is critical.
Drug Release	Tablets	Similar drug release profile as RLD using a predictive dissolution method – OGD media at the following time points: 2h 3 h 4 h 8 h 10h 12h 14h	Yes	The drug release profile is important for bioavailability and bioequivalence (BE); therefore, it is critical. Since *in vitro* drug release is a surrogate for *in vivo* performance, a similar drug release profile to the RLD is targeted to ensure bioequivalence. Formulation and Manufacturing Process may affect DS release.

	Alcohol- induced-dose dumping	Comparable or lower drug release compared to the RLD in 5% (v/v), 20% (v/v), and 40% (v/v) Alcohol USP in HCl 0.1N dissolution medium		The drug release profile in alcohol is critical to patient safety. The target is set to ensure that alcohol stress conditions do not change the bioavailability of the generic product and introduce additional risks to the patient – concomitant consumption of alcoholic beverages along with these products might be expected to have the potential to induce dose dumping.
	Dose Dumping risk	Comparable or lower drug release compared to the RLD in HCl 0.1 N, Acetate pH 4.5 and Phosphate pH 6.8 dissolution medium.		The dissolution profiles in the different media at varying pH´s corresponding to different GI tract conditions on the test product should show evidence of No Risk of dose dumping.
Degradation Products		Reporting threshold: Individual unknown degradation product: NMT 0.2% Total degradation products: NMT 1.0% (to be proposed)	Yes	The limit of degradation products is critical to drug product safety. The limit for individual unknown degradation products complies with ICH Q3B - reporting and qualification threshold cannot be surpassed. A limit for the total degradation products is set based on analysis of the RLD near expiry.
Residual Solvents		Conforms to USP <467> Meet ICHQ3C(R5). limits	No	The drug substance and excipients used in the drug product formulation contain only residual solvents, and the limit can be critical to drug product safety. However, no organic solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards. Levels of ICH Q3C (R5) cannot be surpassed.
Water Content		To be defined according to the RLD characteristics and knowledge of the product	No	Limited amounts of water in oral solid dosage forms will not impact patient safety or efficacy. Therefore, it is not critical.
Microbial Limits		Meets relevant pharmacopoeia criteria. Meet ICHQ4B(4C). limits	No	Non-compliance with microbial limits will impact patient safety. However, as long as raw materials comply with compendial microbial requirements, the formulation and process variables are unlikely to impact this CQA. Water activity will be tested on the final prototype formulation to confirm that the drug product does not support microbial growth. Formulation and manufacturing process unlikely to affect.

3.2. Characterization of drug product

3.2.1. Drug Substance

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., solid state properties), should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be inter- related and might need to be considered in combination.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted. The knowledge gained from the studies investigating the potential effect of drug substance properties on drug product performance can be used, as appropriate, to justify elements of the drug substance specification.

The compatibility of the drug substance with excipients should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated. (ICH Q8(R2), August 2009). The compatibility studies will be discussed in 3.2.2. section.

The following table show a risk assessment of a drug substance done by a development project:

Table 8 *- Risk Assessment of Drug Substance*

Drug Product CQAs	Drug Substance Attributes									
	Solid State Form	Particle Size Distribution (PSD)	Particle Shape	Hygroscopicity	Solubility	Moisture Content	Residual Solvent	Chemical Stability /Process Impurities	Optical Rotation	Flow Properties
Assay	Low	Medium	Low	Low	Low	Low	Low	High	Low	Low
Content Uniformity	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Medium	High	Low	Low	Medium	Low	Low	Low	Low	Low
Degradation Products	Medium	Low	Low	Low	Low	Medium	Low	High	Low	Low
Tablet production	Low	Medium	Medium	Low	Low	Low	Low	Low	Low	Medium
PK/PD*	Medium	Medium	Low	Low	Medium	Low	Low	High	High	Low

Table 9 - *Justification of risk assessment of drug substance*

Drug Substance Attributes	DP CQAs	Justification
Solid State Form	Assay	Drug substance solid state form does not affect tablet assay and content uniformity. **The risk is low**.
	CU	
	Dissolution	The form of DS hemihydrate was reported in US patent X, and the DS manufacturer DMF states that the DS manufactured by XY conforms to the polymorphism reported in patent. It present Pseudopolymorthism as under extreme dry conditions the bounded water can be removed to give anhydrous form, but on rehydration it rapidly transforms the API in the hemihydrate form. Nevertheless, different polymorphic forms of the drug substance may have different solubility and can impact tablet dissolution Thus, further clarification/evaluation of polymorphic form must be addressed. **The risk can be considered medium.**
	Degradation Products	Drug substance with different polymorphic forms may have different chemical stability and may impact the degradation products of the final dosage form. Thus, further clarification/evaluation of polymorphic form must be addressed. **The risk can be considered medium.**
	Tablets production	Solid state form of DS has no impact on the performance of the production of tablets. **The risk is low**.
	PK/PD	The form of DS hemihydrate was reported in US patent X and the DS manufacturer DMF states that the DS hemihydrate manufactured by XY conforms to the polymorphism reported in patent. However, solid state form can affect dissolution profile and thereafter can affect bioavailability. **The risk is considered medium.**

DS Attributes	Drug Products CQAs	Justification
Particle Size Distribution (PSD)	Assay	The PSD can impact the blend pharmacotechnical properties. A small particle size may adversely impact blend flowability. In extreme cases, poor flowability may cause an assay failure and also a content uniformity failure. DS represents from 12% to around 30% of the active layer formulation, thus its particle size is critical for the development of the drug product. However, the manufacturing process involves a wet granulation step, which promotes the change of the pharmacotechnical properties of the original DS and of the final blend. Further evaluation of PSD on drug product attributes is to be considered. **The risk is considered medium.**
	CU	
	Dissolution	According to available information, the DS is soluble in different media, but as the Drug Product is of sustained release, the PSD can affect dissolution/DS release. The impact of PSD on the dissolution profile should be thoroughly evaluated. **The risk is considered high.**
	Degradation Products	It is not expected that PSD will have a significant impact on product degradation levels. **The risk is considered low**.
	Tablets production	Even though the proposed manufacturing process is a wet granulation with the use of binding agents for the formation of granules, the PSD of the DS can impact the manufacturing process, namely granulation and tableting. **The risk is considered medium.**
	PK/PD	Again, particle size distribution can affect DP release performance. This is particularly important for drugs with controlled release profile. **The risk is medium.**
Particle Shape	Assay	The particle shape can impact the blend pharmacotechnical properties. Needle shaped or other ribbon-shaped particles may influence powder flowability. In extreme cases, poor flowability may cause an assay failure. However, the manufacturing process involves a wet granulation step, which promotes alteration of the pharmacotechnical properties of the original DS and of the final blend. **Thus the risk is considered Low**.
	CU	
	Dissolution	Needle shaped or other ribbon-shaped particles may influence powder compressibility and ultimately impact drug product dissolution. However, the manufacturing process involves a wet granulation step, which promotes alteration of the pharmacotechnical properties of the original DS and of the final blend. **Thus, the risk is considered Low.**
	Deg.Prod.	It is not expected that particles shape will have a significant impact on product degradation levels. **The risk is considered as low.**
	Tablets production	Particle shape may affect powder pharmacotechnical properties, namely flowability and compressibility. Needle shaped or other ribbon-shaped particles may lead to different powder characteristics, affecting the outcome of the finished product manufacturing process. **The risk is considered medium.**
	PK/PD	Particle shape does not affect directly the PK/PD of final drug product. **The risk is low.**

Hygroscopicity	Assay	DS is considered not hygroscopic. No impact is expected on the assay, content uniformity, dissolution and on the degradation products. Additionally, tablets dissolution and PK/PD of the final drug product is unrelated to DS hygroscopicity.**The risk is low.**
	CU	
	Dissolution	
	Degradation Products	
	Tablet production	
	PK/PD	
Solubility	Assay	Solubility does not affect tablet assay, content uniformity and degradation products. **The risk is low.**
	CU	
	Degradation Products	
	Dissolution	DS solubility can affect dissolution/DS release. At 25°C, DS hemihydrate is slightly soluble in water, soluble in methanol and alcohol. When the acidity of the solution increase from pH 1 to 6, the capacity of solubility of DS hemihydrate increase from practically insoluble to slightly soluble. At pH 7 to 9, DS hemihydrate is practically insoluble. It is important to clarify the values of solubility at different physiological pHs, in order to assess the impact in dissolution profiles. This topic must be further clarified. **The risk is medium.**
	Tablets production	Solubility is unrelated with DS production. **The risk is low.**
	PK/PD	Solubility in different solvents is an intrinsic characteristic for a defined molecule. The aqueous solubility is a major indicator for the solubility in the intestinal fluids and its potential contribution to bioavailability issues. The same Drug Substance Salt as compared with the RLD is used on the X project, minimizing the risk of BDBE failure due to differences in DS solubility. **The risk is medium.**
Moisture Content	Assay	Moisture is controlled within tight limits in the drug substances specifications (2.2% to 2.8%). DS is considered not hygroscopic. However, manufacturing process of drug product involves wet granulation step, with the elimination of the water added, and therefore loss on dry of the granulated should be controlled during the manufacturing process. **The risk is considered as low**.
	Content Uniformity	
	Dissolution	
	Degradation Products	DS is considered not hygroscopic. It is important to attend to the storage conditions of the DS, and define the DS stability to Moisture. Moreover, the moisture content of the final drug product should be controlled. **The risk is considered as medium.**
	Tablet production	Moisture is controlled within tight limits in the drug substances specifications (2.2% to 2.8%). DS is considered not hygroscopic. However, manufacturing process of drug product involves wet granulation step with subsequent elimination of the solvent / water. This way the loss on dry of the granulated should be controlled. **The risk is considered Low.**
	PK/PD	Moisture does not affect directly the PK/PD of final drug product. **The risk is considered low.**
Residual Solvents	Assay	Residual solvents are controlled in the drug substance specification and comply with USP 37. At ppm level, residual solvents are unlikely to impact assay, CU, dissolution and degradation products. **The risk is considered as low.**
	Cont. Unif.	
	Dissolution	
	Deg. Prod.	
	Tablets production	
	PK/PD	

Chemical Stability / Process impurities	Assay	According to the DMF, results obtained for the studies performed for DS Hemihydrate in solid state it can be stated that no degradation was observed under tested conditions of humidity, heat and light exposure. Additionally, no significant change in the appearance of the sample was observed for these stress conditions. Based on the results obtained for the studies performed in solution it can be stated that no significant degradation was observed under acid hydrolysis. A minor degradation was observed under base hydrolysis, oxidation and heat conditions. A degradation of about 15% was observed under light exposure conditions when the sample is in solution. The drug substance supplied is consistently pure with total impurities below specified limits. This way, Assay is to be monitored during drug product production and stability. **The risk is considered as high.**
	CU	Dosage form content uniformity is unrelated to drug substance chemical stability. **The risk is considered as low.**
	Dissolution	Tablet dissolution is unrelated to drug substance chemical stability. **The risk is considered as low.**
	Deg. Prod.	Chemical stability may cause significant impact on drug product degradation. Impurity profile and degradation will be monitored within the formulation and process development. **The risk is high.**
	Tablets production	Chemical stability is not related with tablets production. **The risk is low.**
	PK/PD	Chemical stability of DS can affect the assay and consequently the bioavailability. Additionally, it is not desirable the presence of impurities at a level superior of certificate of analysis specifications. This is valid for the drug substance and thereafter for the final drug product. **The risk is considered high.**
Optical rotation	Assay	DS Optical Rotation is not related with Assay, Impurities, dissolution nor production process. **The risk is considered low.**
	Content Uniformity	
	Dissolution	
	Degradation Products	
	Tablets production	
	PK/PD	It is known that enantiomers have different pharmacokinetic (metabolism/elimination) and different pharmacodynamics (S-enantiomer is a more potent than R- enantiomer). There are two asymmetrical carbon atoms present in the structure of DS, and theoretically, there are four enantiomers possible. Actually, there are only two enantiomers, (3R, 4S)-isomer and (3S, 4R)-isomer. (3S, 4R) isomer is the wanted product, and the other isomer (3R, 4S)-isomer is original from the starting material (3S, 4R) Alcohol compound, which is an impurity. The impurity (3S, 4R) isomer ((+)-trans isomer) in XY finish product are determined by a HPLC method and set up the limit NMT 0.10% as per USP, and should be controlled on the DP. **The risk is High.**

Flow Properties	Assay	Flow properties of the drug substance can have a significant impact in the production process, as well as on the quality of the drug product. Although the amount of DS to be used on the formulation is only from around 12% to around 30%, the pharmacotechnical properties of the drug product can be impacted by the drug substance characteristics used on the process. However, the manufacturing process involves a wet granulation step with the addition of a binder and formation of granules, which promotes alteration of the pharmacotechnical properties of the original DS and of the final blend and thus on the final drug product quality. **This way the risk is Low.**
	CU	
	Dissolution	Flow properties of the DS do not impact the dissolution or the appearance of impurities. **The risk is Low.**
	Degradation Products	
	Tablets production	Flow properties of the drug substance can have a significant impact in the production process, as well as on the quality of the drug product. Even though the amount of DS to be used on the formulation is not high, the pharmacotechnical properties of the drug product can be impacted by the drug substance characteristics used on the process. Flow properties may affect significantly powder compressibility, affecting the outcome of the finished product. However, the manufacturing process involves a wet granulation step with the addition of a binder and formation of granules, which promotes alteration of the pharmacotechnical properties of the original DS and of the final blend and thus on the final drug product quality. Nevertheless, this topic should be addressed. **The risk is medium.**
	PK/PD	Flow properties of DS does not affect PK/PD of final drug product. **The risk is low**

The Critical Drug Substance Attributes to be monitored in this specific project should be:

- Solid State Form
- Particle shape (optical microscopy)
- Particle Size Distribution (PSD)
- Solubility
- Chemical Stability
- Moisture content
- Optical Rotation
- Flow properties

3.2.1.1.BCS Classification

Biopharmaceutics classification system (BCS) is a scientific classification of a drug substance based on its aqueous solubility and intestinal permeability that correlates in vitro dissolution and in vivo bioavailability of drug products (G.L. Amidon, 1995). When combined with in vitro dissolution characteristics of the drug product, BCS takes into account two major factors: solubility and intestinal permeability, which govern the rate and extent of oral drug absorption from solid dosage forms and ultimately, its bioavailability (L.X. Yu, 2002). Due to this reason, BCS is the fundamental tool in the drug development especially in the development of oral drug products. (science direct, 2016)

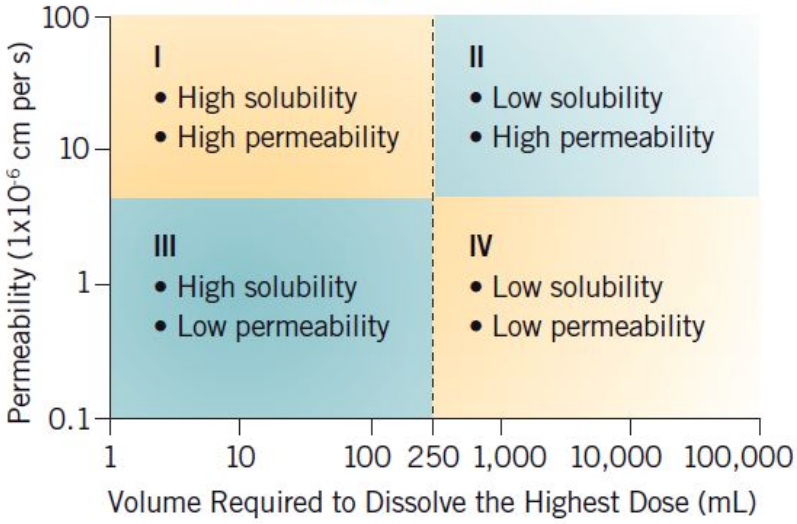

Figure 3 *- BCS Classification (particle sciences)*

The food and drug administration (FDA) criterion for solubility classification of a drug in BCS is based on the highest dose strength in an immediate release (IR) oral product (L.X. Yu, 2002). A drug is considered highly soluble when the highest strength is soluble in 250 ml (this volume is derived from typical bioequivalence study protocols) or less of aqueous media over the pH range of 1.0–7.5; otherwise the drug substance is considered poorly soluble. On the other hand, the permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of the mass transfer across the human intestinal membrane, or in animals, or in vivo models (L.X. Yu, 2002). A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher based on mass-balance or in comparison to an intravenous reference dose.

The bioavailability of BCS class II drugs is likely to be dissolution rate limited. But due to their high permeability, the BCS class II drugs have been on focus for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed (S. Onoue, 2012). In case of class III drugs, the bioavailability is permeability-rate limited, but dissolution is likely to occur rapidly. Thus for class III drugs, formulating IR solid dosage forms with absorption enhancers can be a viable formulation option to improve their permeability (Y. Kawabata, 2011). But in case of BCS class IV compounds, the bioavailability is limited by both dissolution as well as intestinal permeability. Because of low membrane permeability, BCS class IV drugs are often poor candidates for drug development since solubility and dissolution enhancement alone might not help improve their bioavailability. However, these classes of compounds cannot be ignored just because of their permeability issues. Therefore the current approaches being used for BCS class II drugs, together with absorption enhancers, can be applied to formulate class IV compounds (Y. Kawabata, 2011). Another formulation development approach for class IV compounds is the selection of a better drug candidate with more appropriate physiochemical properties during the lead optimization phase (A. Fahr, 2007). (science direct, 2016)

3.2.2. Excipients

Pharmaceutical powder technology deals with the examining of materials, formulations, additives and processes on achieving the desired properties or performance of the particles or composites (R.N. Davé, 2013). Particle properties of active drug substances or excipients play an important role in the dosage form fabrication and performance. Pharmaceutical powder technology also deals with areas of surface engineering usually explored through the applications of surface chemistry and surface morphology. Overall, the properties like particle shape, size, adhesiveness, morphology, roughness, wettability, density, surface chemistry, plasticity, hardness, brittleness and hygroscopicity are important for successful dosage form design and development. Ultimately, these strategies are implemented to produce a drug product that is readily soluble in the GI tract because incomplete dissolution in the GI tract can severely restrict their oral bioavailability drug compounds (J.B. Dressman, 2007).

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not. Compatibility of excipients with other excipients, where relevant (for example, combination of preservatives in a dual preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated. The information on excipient performance can be used, as appropriate, to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification.

Information to support the safety of excipients, when appropriate, should be cross-referenced. (ICH Q8(R2), August 2009)

The compatibility study of the excipients with the drug substance is very important to define the stability of the formulation and define the preliminary quantitative and qualitative composition of the drug product. The following tables represent an example of a compatibility study design.

Table 10 *- Design of Compatibility test (1)*

Sample Presentation	25ºC / 60% RH	40ºC / 75% RH	Rationale
Individual components	**Open and Closed Flask** (only test if necessary)	**Open and Closed Flask** (only test if necessary)	The objective is to analyze only if inconclusive results are obtained in the combined mixtures.
Binary mixtures	**Open and Closed Flask**	**Open and Closed Flask**	The objective is to test the compatibility profile of the combined mixtures under forced degradation and long term stability conditions.
Time points	T=1M and T=3M.	T=1M and T=3M.	Two time points are enough to take out conclusions.

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Table 11 *- Design of Compatibility test (2)*

Sample ID	0 day	1 Month				3 Months			
		25/60		40/75		25/60		40/75	
Type of analysis		Open Flask	Closed Flask	Open Flask	Closed Flask	Open Flask	Closed Flask	Open Flask	Closed Flask
S (DS) 12.5mg	T0	S1	S2	S3	S4	S5	S6	S7	S8
A Excipient A	-	*A1*	*A2*	*A3*	*A4*	*A5*	*A6*	*A7*	*A8*
B Excipient B	-	*B1*	*B2*	*B3*	*B4*	*B5*	*B6*	*B7*	*B8*
C Excipient C	-	*C1*	*C2*	*C3*	*C4*	*C5*	*C6*	*C7*	*C8*
D Excipient D	-	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*
E Excipient E	-	*E1*	*E2*	*E3*	*E4*	*E5*	*E6*	*E7*	*E8*
F Excipient F		*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
G Excipient G + Excipient H + Excipient I		*G1*	*G2*	*G3*	*G4*	*G5*	*G6*	*G7*	*G8*
H S + A - 1:1	-	H1	H2	H3	H4	H5	H6	H7	H8
I S + B - 1:1	-	I1	I2	I3	I4	I5	I6	I7	I8
J S + C - 1:1	-	J1	J2	J3	J4	J5	J6	J7	J8
K S + D - 1:1	-	K1	K2	K3	K4	K5	K6	K7	K8
L S + E - 10:1	-	L1	L2	L3	L4	L5	L6	L7	L8
M S + F – 10:1	-	M1	M2	M3	M4	M5	M6	M7	M8
N	-	N1	N2	N3	N4	N5	N6	N7	N8

The ratio used for compatibility is based on tablets strength, considering a worst case scenario where a higher presence of excipient with DS occur.

The samples were placed in climatic chambers at 25ºC/60% RH (long-term conditions) and at 40ºC/75%RH (forced degradation conditions) and the analytical results were compiled to better understand if any excipient have impact in the degradation of drug substances.

3.3. Manufacturing Process

The selection, the control, and any improvement of the manufacturing process (i.e., intended for commercial production batches) should be explained. It is important to consider the critical formulation attributes, together with the available manufacturing process options, to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process improvement, process validation, continuous process verification (where applicable), and any process control requirements. Where appropriate, such studies should address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification.

The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality.

Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials (safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the process should be discussed. The discussion should summarise the influence of the differences on the performance, manufacturability and quality of the product. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information. The information should include, for example, (1) the identity (e.g., batch number) and use of the batches produced (e.g., bioequivalence study batch number), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

To provide flexibility for future process improvement, when describing the development of the manufacturing process, it is useful to describe measurement systems that allow monitoring of critical attributes or process end-points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process control strategies that provide process adjustment capabilities to ensure control of all critical attributes should be described.

An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating

conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness can be useful in risk assessment and risk reduction and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools. (ICH Q8(R2), August 2009)

Presently, Bluepharma carry out manufacturing operations of non-sterile products / solid dosage forms - capsules and tablets. The site is also authorized by the Portuguese Health Authority to produce semi-solids, liquids for internal use, suppositories and investigational medicinal products.

Several manufacturing process technologies can be used at production and laboratorial facilities in Bluepharma, such as:

- Mixture/Blending;
- Wet Granulation;
- Dry Granulation;
- Tabletting, including microtablets and bilayer technology;
- Encapsulation of powder, pellets and microtablets;
- Coating;
- Hot Melt Extrusion.

During development of a new generic drug product is common to find in the bibliography and patent analysis the type of manufacturing process used for the manufacturer´s of reference product. Information of qualitative formulation can also help to define the type of manufacturing technology which should be used (some excipients are almost exclusively used in a particular manufacturing process). Despite of that, the study of manufacturing process usually begins with direct compression (an easier and cheaper process) and escalates to more complex and challenging processes. After found a process with promising analytical results (such as drug release, assay and related substances), the process can be finally optimised following a quality by design approach.

The following table represents a manufacturing risk assessment done for a development of a new generic drug product. After defining the critical process steps, they will be studied to minimize the risk for the quality of the final product.

Table 12 - Manufacturing Risk Assessment

Drug Product CQAs	Process Steps																					
	Room Conditions		Dry Excipients Mixing		Wet Granulation							Wet Sieving		Drying		Granules Sizing	Pre-Blend			Final Blending /Lubrication		
Process Parameters	Temperature	Humidity	Time of mixing	Mixer Speed	Geometry of impeller	Volume/% occupation	Amount of solution added	Solution Addition time	Mixer Speed	Chopper Speed	Total time of granulation process	Bowl Discharge	Sieve Size	Temperature	Final LOD	Sieve Size	Geometry of Blender	Time of Mixing	Rotation Speed	Time of Mixing	Rotation Speed	Bin Discharge
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	High	High	High	Low	Low	High	Low	Low	Low	Medium	High	Low	Low	Low	High	Low	Low
Degradation Products	Low	Low	Low	Low	Low	Low	Medium	Low	Low	Low	Low	Low	Low	Medium	Medium	Low	Low	Low	Low	Low	Low	Low

Table 13 - Justification of manufacturing risk assessment

Manufacturing Steps	Parameters	Drug Product CQAs	Risk	Justification
Room Conditions at Wet Granulation, Drying, sizing and blending	Temperature and Humidity	Assay	Low	If not controlled, fluctuations in the facility temperature and RH could impact Drug product CQAs. Nevertheless, routine environment temperature and RH set point in the GMP manufacturing facility is fixed at 25ºC ± 5% and 40% - 60% respectively, and will be monitored during manufacturing. **The risk is Low**
		Mixture Homogeneity	Low	
		Dissolution	Low	
		Degradation Products	Low	
Dry Excipients Mixing	Time of Mixing	Assay	Low	Simple blending process intended to promote initial DS homogenization, prior to wet granulation. Further wet granulation step will take place, promoting DS homogeneity within the granulate. This parameter is not critical for Assay, Dissolution and Impurities. **The risk is Low**
		Dissolution	Low	
		Degradation Products	Low	
		Mixture Homogeneity	Medium	Even though it is a simple mixing step to promote initial DS homogenization, prior to wet granulation step, this should promote some initial DS homogeneity to ensure proper final product quality. **The risk is Medium**
	Mixer Speed	Assay	Low	The mixer speed is fixed in galenical laboratory equipment to meet the fixed speed of industrial equipment, and this speed was used during QbD tests. No different speed is expected to be used. **The risk is Low**
		Mixture Homogeneity	Low	
		Dissolution	Low	
		Degradation Products	Low	
Wet Granulation	Geometry of impeller	Assay	Low	The geometry of the paddle of the impeller in galenical Lab is the same as used on production.This parameter is not critical. **The risk is Low**
		Mixture Homogeneity	Low	
		Degradation Products	Low	
		Dissolution	Low	
	Volume of bowl occupation	Assay	Low	The mixture homogeneity, assay and degradation products are not influenced by granulation bowl occupation, specially due to the high amount of DS on the formulation. **The risk is low.**
		Degradation Products	Low	
		Mixture Homogeneity	Low	
		Dissolution	High	The amount of mass to be granulated can impact the characteristics of the final granules, possibly impacting the DS release under dissolution. **The risk is high.**
	Amount of granulation solution / amount of water added	Dissolution	High	The amount of water can impact the granules characteristics and thus dissolution of the DP. This parameter is critical for the process and for that reason should be tested. **Risk is High**
		Assay	Low	It is not expected that amount of water added in granulation can impact the assay and mixture Homogeneity, specially due to the high amount of DS on the formulation. **The risk is low.**
		Mixture Homogeneity	Low	

		Degradation Products	**Medium**	In this particularly case, since the API is not sensitive to moisture, there is no impact of amount of water added in granulation in degradation products. Nevertheless, the impact of water added on DP stability is to be verified. **The risk is medium.**
	Granulation solution addition time	Assay	**Low**	The mixture homogeneity, assay and degradation products are not influenced by granulation solution addition time, specially due to the high amount of DS on the formulation. **The risk is low.**
		Mixture Homogeneity	**Low**	
		Degradation Products	**Low**	
		Dissolution	**High**	The time of addition of granulation solution can impact the characteristics of the granules and thus final mixture, and possibly impacting the DS release under dissolution. **The risk is high.**
	Mixer Speed	Assay	**Low**	The mixer speed was fixed in galenical laboratory equipment to meet the fixed speed of industrial equipment, and this speed was used during QbD tests. No different speed is expected to be used. **The risk is Low**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation Products	**Low**	
	Chopper Speed	Assay	**Low**	The chopper is to be used during development tests and set to accommodate powder flow inside the bowl and promote proper wet granules milling, optimizing granulation process and to be used in order to eliminate agglomerates formation. **The risk is Low**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation Products	**Low**	
	Total time of granulation process	Dissolution	**High**	Wet kneading time can impact the DP performance / characteristics, namely dissolution profile and tablets pharmacotechnical properties (flow, tendency to sticking, hardness and friability). This is potentially critical. **The risk is High**
		Assay	**Low**	The mixture homogeneity, assay and degradation products are not influenced by total wet kneading time. **The risk is low.**
		Mixture Homogeneity	**Low**	
		Degradation Products	**Low**	
Wet Sieving	Bowl Discharge	Dissolution, Assay, Mixture Homogeneity, Degradation Products	**Low**	As the manufacturing process is a wet granulation with the formation of granules, it is not expected that the DS or excipients get segregated during manipulation, also with no impact on degradation products or dissolution. **The risk of this step is Low.**
	Sieve Size	Assay	**Low**	This simple sieving step through a large sieve is used to break any agglomerate present on the wet granules, in order to facilitate the drying of the granules. **The risk of this step is Low.**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation	**Low**	
Drying	Temperature of Drying	Assay	**Low**	Drying Temperature is unlikely to impact Assay, Content Uniformity or Dissolution. **The risk is Low.**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	

		Degradation Products	**Medium**	If the product is sensitive to temperature, the stability can be affected by drying step. Nevertheless, forced degradation tests performed on the DS indicated no degradation of the DS when submitted to heat. In any case, in order to mitigate any risk, degradation of the product should be investigated at different drying temperatures. **The risk is Medium**
	Final LOD	Assay	**Low**	Final LOD do not impact Assay and Mixture homogeneity. **The risk is Low**.
		Mixture Homogeneity	**Low**	
		Dissolution	**Medium**	Final LOD will impact the water present in the final mixture. Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. In this case, DS is not sensitive to hydrolysis and moisture. However, different values of LOD will be tested as also as it's impact on stability of the product. **The risk is medium**
		Degradation Products	**Medium**	
Granules Sieving	Sieve Size	Assay	**Low**	The milling step controls the final granule size distribution. A suboptimal distribution may affect flow, causing variable tablet weight and assay during compression. If milling generates excessive fines, both bulk density and flowability of the blend may be impacted, impacting CU. Nevertheless, the process leads to granules with good flow, and it is not expected to be impacted. **The risk is Low**
		Mixture Homogeneity	**Low**	
		Dissolution	**High**	If milling generates excessive fines or coarse particles, may impact DS release/dissolution profile. **The risk is High.**
		Degradation Products	**Low**	Although the screen may heat up during the milling process, the dwell time is brief. Milling is unlikely to impact degradation products. **The risk is low.**
Pre-Blend	Geometry of blender	Assay	**Low**	The geometry of the blender on galenical Lab is the same used in production. This parameter is not critical. **The risk is Low**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation Products	**Low**	
	Time of Mixing	Assay	**Low**	The time of blending for homogenization of granules and Silica Colloidal does not affect the dissolution and the impurities of the formulation. Generally, the time of blend can have impact on the homogeneity of the mixture and consequently in the assay and content uniformity of the tablets, but on this case this step is only to homogenize the granulate, and no risk of heterogeneity is present. This step is considered **Low Risk**.
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation Products	**Low**	
	Speed of Mixer	Assay	**Low**	Rotation speed is fixed by equipment constraint. The rotation speed used in Galenical Lab is equivalent to the rotation speed used in production. No different speed is available. Not critical. **The risk is Low**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation Products	**Low**	

Final Blend	Time of Lubrication	Assay	**Low**	As the manufacturing process is wet granulation, over-lubrication is not expected to lead to loss of homogeneity. This step is considered **Low Risk** for assay and content uniformity.
		Mixture Homogeneity	**Low**	
		Dissolution	**High**	Over-lubrication due to an excessive number of revolutions may impact disintegration and dissolution of the tablets and ultimately the DP performance. Therefore **the risk is High.**
		Degradation Products	**Low**	It is unlikely that lubrication impact degradation products. **The risk is low**
	Rotation Speed	Assay	**Low**	Rotation speed is fixed by equipment constraint. The rotation speed used in Galenical Lab is equivalent to the rotation speed used in production. No different speed is available. Not critical. **The risk is Low**
		Mixture Homogeneity	**Low**	
		Dissolution	**Low**	
		Degradation Products	**Low**	
	Bin Discharge	Dissolution, Assay, Mixture Homogeneity, Degradation Products	**Low**	As the manufacturing process is a wet granulation, it is not expected that the DS gets segregated during manipulation, also with no impact on degradation products or dissolution. **The risk of this step is Low.**

The Critical Drug Substance Attributes to be monitored in this project regarding the manufacturing process should be:

- The impact of time of mixing of dry excipients in content uniformity;
- The impact of Volume of occupation, amount of granulation solution added, addition time of granulation solution, total time of granulation process, final LOD, sieve size of granules and time of mixing of final blend in dissolution;
- The impact of the Amount of solution added, temperature of drying, final LOD in degradation products.

To simplify the access of manufacturing process, it is very useful the use of flowcharts during development. The following figure represents an example of a manufacturing process flowchart (until final mixture) of drug product in development.

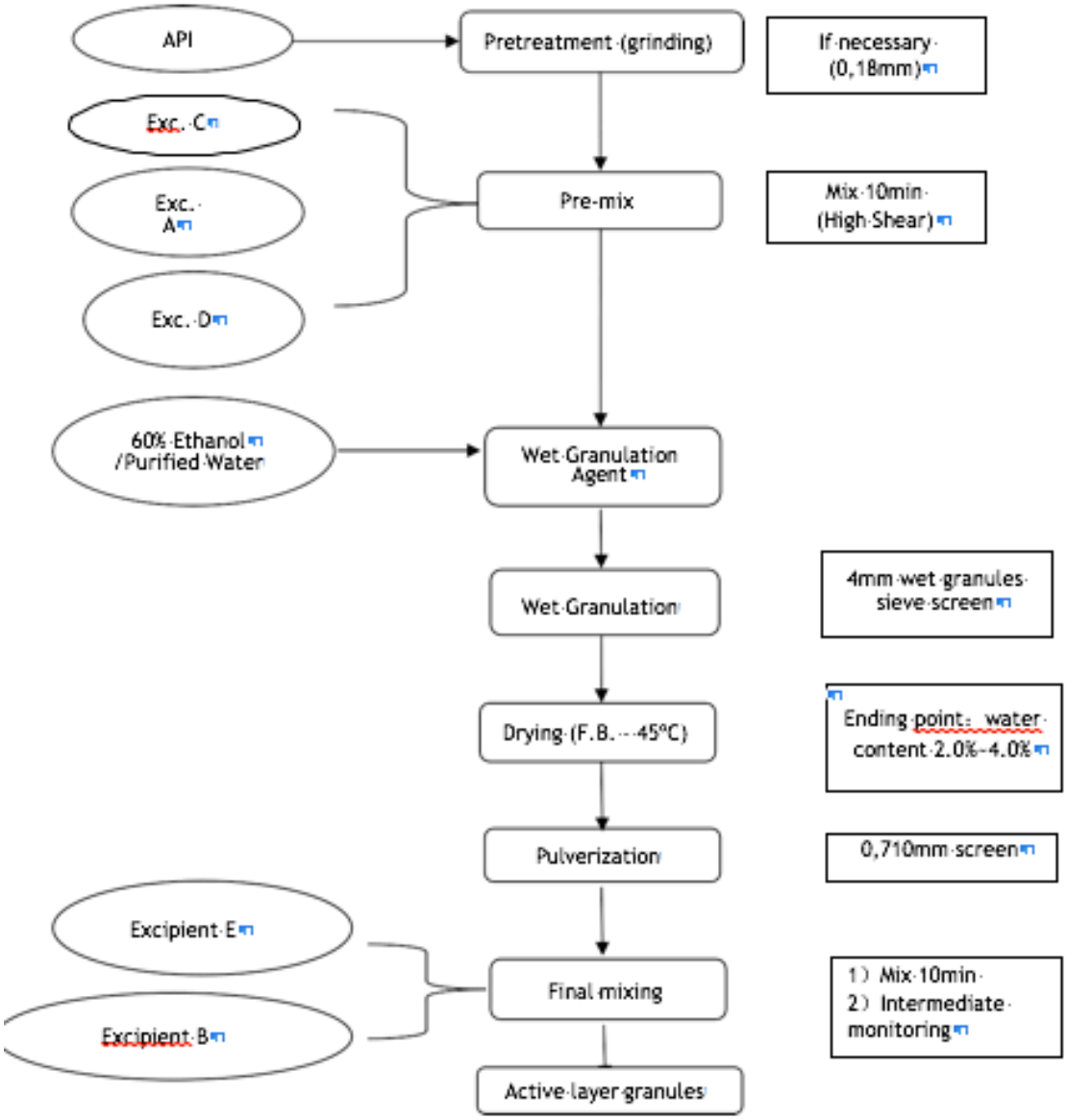

Figure 4 – *Flowchart example of the manufacturing process*

3.4. Formulation Development

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration. Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important to ensure the quality of the drug product.

The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance, excipients, container closure system, any relevant dosing device), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s).

Any excipient ranges included in the batch formula should be justified in this section of the application; this justification can often be based on the experience gained during development or manufacture.

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Information from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) that links clinical formulations to the proposed commercial formulation should be summarized and a cross- reference to the studies (with study numbers) should be provided.

Any special design features of the drug product (e.g., tablet score line, overfill, anti-counterfeiting measure as it affects the drug product) should be identified and a rationale provided for their use. (ICH Q8(R2), August 2009)

The qualitative formulation derives from bibliography and patent analysis. Following the qualitative formulation, a risk assessment study is performed. There the critical points to be studied are identified. With the results obtained a quality by design strategy is created and followed to achieve the final quantitative formulation. This methodical analysis defines limits for the use of excipients according to the quantities described in the bibliography.

The following drug product critical quality attributes (CQAs) were identified for the tablets formulation.

Table 14 - *Risk assessment of formulation*

Excipient	Drug Product Quality Attributes (CQA)				
	Raw Material Attributes	Assay	Related Substances	Dissolution	UDU
A	Level Used	Low	Low	High	Low
	Grade	Low	Low	High	Low
	Loss On Drying [LOD]	Low	Low	Low	Low
	Particle Size Distribution [PSD]	Low	Low	Low	Low
	Batch to Batch Variability	Low	Low	Medium	Low
B	Level used	Low	Low	High	Low
	LOD	Low	Low	Low	Low
	PSD/Specific surface area	Low	Low	Low	Low
	Grade	Low	Low	Low	Low
	Batch-to-Batch Variability	Low	Low	Low	Low
C	Level used	Low	Low	Medium	Low
	PSD	Low	Low	Medium	Low
	Grade	Low	Low	Medium	Low
	Batch-to-Batch Variability	Low	Low	Low	Low
D	Level used	Low	Low	High	Medium
	LOD	Low	Low	Low	Low
	PSD	Low	Low	Low	Low
	Grade	Low	Low	Low	Low
	Batch-to-Batch Variability	Low	Low	Low	Low
E	Level used	Low	Low	Low	Medium
	PSD/Specific surface area	Low	Low	Low	Low
	Batch-to-Batch Variability	Low	Low	Low	Low

Table 15 - Justification of formulation risk assessment

Excipient	Material attributes	CQA	Initial Risk	Justification/Discussion
A	LOD, PSD	Assay, Related Substances, UDU Dissolution	Low	LOD and PSD of Excipient A do not directly influence the CQAs of the drug product, as Excipient A is solubilized in water for the granulation solution. From the drug-excipient compatibility studies, it was noticed that Excipient A is compatible with the DS, not impacting Assay and Related substances. Therefore **this risk is low.**
	Level used	Dissolution	High	Excipient A is selected in the formulation as a binding agent. Due to the binding nature of the excipient, level of Excipient A might influence the dissolution rate of the final dosage form and therefore optimization of level of Excipient A in the formulation is important. **This risk is high.**
		Assay	Low	Amount of Excipient A used does not correlate with DS assay on the drug product, especially considering the high percentage of DS on the formulation. DS-Excipient compatibility test performed indicate no interaction or incompatibility between the DS and Excipient A, and additionally, Excipient A is present on the RLD formulation. Nevertheless, DP stability will be closely controlled throughout development. Therefore **this risk is low.**
		Related Substances	Low	DS-Excipient compatibility test performed indicate no interaction or incompatibility between the DS and Excipient A and additionally, Excipient A is present on the RLD formulation. Nevertheless, DP stability will be closely controlled throughout development. Therefore **this risk is low**
		UDU	Low	Due to the high percentage of DS on the formulation, the homogeneity of active on the final mixture is not impacted by the Excipient A amount. **This risk is Low.**
	Grade / Viscosity	Dissolution	High	Excipient A is generally available as different grades with differences in viscosities. Grade of Excipient A might influence the dissolution rate of the final dosage form due to differences in viscosity. Nevertheless, the suitability of this Excipient A grade is to be verified during development work. **This risk is high.**
		Assay, Related Substances, UDU	Low	Excipient A grade is not related with UDU, Assay or Related Substances. **This risk is low.**
	Batch-to-Batch variability	Assay, UDU, Dissolution, Related Substances	Medium	Large variation of PSD between batches within the grade could impact the process or characteristics of the Drug Product, but Excipient A is totally solubilized on the granulation solution, with PSD having no impact on the product or process. **The risk is medium**
B	Grade, LOD	Assay, UDU, Dissolution, Related Substances	Low	Excipient B is used in the formulation as lubricant to facilitate the compression. The CQAs of finished product do not get affected by the grade and LOD of the magnesium stearate. **The risk is low.**
	PSD/Specific surface area	Assay, UDU, Dissolution, Related Substances	Low	Excipient B is used in the formulation in a very low amount. Standard Pharma grade of Excipient B is to be used. The CQAs of finished product do not get affected by the PSD. **The risk is low.**
	Level used	Related substances, Assay	Low	In DS- Excipient B compatibility study, no Impurities were formed as well as no reduction of Assay was observed on the samples. Additionally, this excipient is present on the RLD. No impact of Excipient B is expected on the Assay nor Impurities. Nevertheless, it is important to control the product stability screening for possibility of degradation. **This risk is Low.**

		Dissolution	High	As Excipient B is a hydrophobic material generally used as a lubricant level might impact the dissolution of dosage form. Therefore, it is important to control the level of Excipient B in the formulation to achieve desired dissolution profile/DP performance. **The risk is High**
		UDU	Low	No impact of Excipient B is expected on the UDU, especially as the amount of DS on the formulation is very high. **This risk is Low.**
		Assay, Related Substances, UDU Dissolution	Low	Large variation of PSD and surface area between batches within the grade could impact the product performance and characteristics, but known experience with the excipient has shown that batch to batch variability is minimal, with no impact on Drug product quality or performance. **The risk is Low**
	Batch-to-Batch variability	Assay, Related Substances, UDU, Dissolution	Low	Large variation of PSD and surface area between batches within the grade could impact the product performance and characteristics, but given the low amount of this components, as well as known experience with the excipient has shown that batch-to-batch variability is minimal, with no impact on Drug product quality or performance. **The risk is Low**
C	Batch-to-Batch vairability	Assay, Related Substances. Dissolution.	Low	Batch-to-Batch variability form of Excipient C do not directly influence the CQAs of the drug product. Available manufacturer data indicated homogeneity between batches, and therefore this risk **is low.**
	Level used	Dissolution	Medium	From the drug-excipient compatibility studies, it was noticed that Excipient C is compatible with the DS. However, being a soluble excipient Excipient C may affect the wetting and therefore the rate of dissolution of the Dosage Form. **This risk is medium.**
		Assay, Related Substances; UDU	Low	From the drug-excipient compatibility studies, it was noticed that Excipient C is compatible with the DS. Level used do not directly influence tire CQAs of the drug product and therefore **This risk is low.**
	Grade, PSD	Dissolution	Medium	Excipient C is generally available in different grades with differences of PSD/Flow properties. As the developed drug product is a sustained release, the grade of Excipient C might influence the dissolution in the final dosage form due to differences in physical attributes, especially PSD and bulk densities, of lactose grade. **The risk is medium**.
		Assay, Related Substances; UDU	Low	Excipient C Grade is not expected to influence the CQAs of the drug product and therefore **this risk is low**.
D	LOD, PSD	Assay, Dissolution, UDU, Related Substances	Low	From the drug-excipient compatibility studies, it was noticed that Excipient D is compatible with the DS. LOD, PSD, and solid stale form of Excipient D do not directly influence the CQAs of the drug product and therefore **this risk is low**.
	Level used	Dissolution	High	Excipient D is selected in the formulation as a binding agent. Due to the binding nature of the excipient, level of Excipient D might influence the dissolution rate of the final dosage form and therefore optimization of level of Excipient D in the formulation is important. **This risk is high**.
		UDU	Medium	The granule quality, in terms of PSD, homogeneity of active, and flow-properties, is influence by the level of Excipient D used formulation. **This risk is medium**.
		Assay, Related Substances	Low	The level used does not influence the CQAs of the finished dosage form. **This risk is low**

	Grade	Dissolution	Medium	Excipient D is generally available as different grades with differences in viscosities. Grade of Excipient D might influence the dissolution rate of the final dosage form due to differences in viscosity. **This risk is medium**.
		Assay, UDU, Related Substances	Low	The grade used does not influence the CQAs of the finished dosage form. **This risk is low**
	Batch-to-Batch Variability	Assay, Dissolution, UDU, Related Substances	Low	Given the low amount used, as well as the homogeneity between the excipient batches, Batch-to-Batch Variability is not expected to influence the CQAs of the finished dosage form. **This risk is low**
E	PSD, Batch to Batch Variability	Assay, Dissolution, UDU, Related Substances	Low	From the drug-excipient compatibility studies, it was noticed that Excipient E is compatible with the DS. Excipient E is used in the formulation as a glidant to facilitate the flow of the granules. Within the normal range of use, this excipient does not influence the CQAs of the finished dosage form. **This risk is low**
	Level used	UDU	Medium	The flow properties of the granules are influenced by grade and PSD of Excipient E and may influence the UDU. **This risk is medium**
		Assay, Dissolution, Related Substances	Low	The level used does not influence the CQAs of the finished dosage form. **This risk is low**

Based on the initial Formulation risk analysis performed, the excipients attributes to achieve the desired DP performance are:

- Excipient A – Amount used
- Excipient A - Grade should also be discussed and possibly investigated
- Excipient A - Batch to batch variability
- Excipient B - Amount used.
- Excipient C - PSD and Amount used
- Excipient D - Amount used
- Excipient E - Amount used

The following drug product critical quality attributes (CQAs) were identified for the tablets formulation.

3.5. Optimization of Formulation Development Vs. Manufacturing Process

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

Pharmaceutical development should include a control strategy. An enhanced, quality by design approach to product development would include the following elements:

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including;
- Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs;
- Determining the functional relationships that link material attributes and process parameters to product CQAs;
- Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing.

As result, this more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle.

A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability. Sources of variability that can impact product quality should be identified, appropriately understood, and subsequently controlled. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an

opportunity to shift controls upstream and minimise the need for end product testing. Product and process understanding, in combination with quality risk management, will support the control of the process such that the variability (e.g., of raw materials) can be compensated for in an adaptable manner to deliver consistent product quality.

This process understanding can enable an alternative manufacturing paradigm where the variability of input materials could be less tightly constrained. Instead it can be possible to design an adaptive process step (a step that is responsive to the input materials) with appropriate process control to ensure consistent product quality.

Enhanced understanding of product performance can justify the use of alternative approaches to determine that the material is meeting its quality attributes. The use of such alternatives could support real time release testing. For example, disintegration could serve as a surrogate for dissolution for fast-disintegrating solid forms with highly soluble drug substances. Unit dose uniformity performed in-process (e.g., using weight variation coupled with near infrared (NIR) assay) can enable real time release testing and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards. Real time release testing can replace end product testing, but does not replace the review and quality control steps called for under GMP to release the batch.

A control strategy can include, but is not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
- In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);

A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models. A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission. (ICH Q8(R2), August 2009)

Presently, in development companies the development strategy is the combination of an empirical development and a systematic development (quality by design). Initially, a general analysis of the project allows to understand the intricacies of the product in hand (e.g. flow properties of the API, solubility of the API, manufacturing process intended to be used, etc.). Later in the development, a quality by design approach can be used leading to an optimization of the process and sometimes to an optimization of the quality of the final product. The quality by design approach also allows to understand the limits of the process, defining in that way the design space where is possible change variables without impact the final quality of the product.

3.6. Scale-up and GMP Production

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach and ongoing continual improvement. (ICH Q10, 2008)

The commercial manufacturing process must be identical to the process used during development and especially during production of material used in late studies. Otherwise, there must be additional studies, resulting in increased development costs and time (FDA, U.S, 2004). The transfer of the production process from development to commercial production is often sped up in order not to waste time and hit the market as soon as possible. The transfer is thus often done in a rudimentary manner, with the main aim only being enabling basic commercial production. This often results in inefficient commercial processes and thus excessive manufacturing costs. Major adaptations to commercial scale equipment and environment are omitted to not further increase time-to-market.

The early integration of production during development allows ensuring in an early phase that the developed processes can be efficiently implemented in a commercial scale and with commercial-scale equipment. Data from practical examples demonstrate that stronger collaboration of development and production in companies leads to more efficient processes. The more advanced a company becomes in integrated development, the earlier processes are adapted and optimized to the commercial scale environment. Ideally, the processes transferred into commercial production do not need any further optimization and do not cause excessive manufacturing costs. In the pharmaceutical industry, development and production are separated and work more or less as silo-organizations. Through an improved collaboration, manufacturing costs could be significantly decreased. Furthermore, the continuous increase of development costs and time is halted.

A structured concept adapted to a company's current set-up facilitates intensified collaboration of both Development and Production and leads to the following process-related or technical advantages:

- Manufacturing processes are not adapted as late as technology transfer; instead, future manufacturing characteristics are considered earlier during process development and scale-up.

- Early consideration of commercial manufacturing environment and equipment as well as a more scientific approach to process development lead to more efficient manufacturing processes.
- Efficient manufacturing processes have a direct positive influence on manufacturing costs. In addition, less post-launch adaptations arise and process. (Ziegler, 2014)

Overall, the goals of manufacturing activities include achieving product realisation, establishing and maintaining a state of control and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded. (ICH Q10, 2008)

4. IMPD Submission to Clinical Trial

Article 2(d) of Directive 2001/20/EC defines a IMP as follows:

'A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.' (European Investigational Medicinal Product Dossiers).

The IMP dossier (IMPD) gives information related to the quality of any IMP (i.e. including reference product and placebo), manufacture and control of the IMP, and data from non-clinical studies and from its clinical use.

It should be clearly differentiated between the requirements for a dossier for a clinical trial and a marketing authorisation dossier. Whilst the latter ones have to ensure a state-of-the-art quality of a product for wide use in patients, information to be provided for investigational medicinal products (IMPs) should focus on the risk aspects and should consider the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself. (Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. (2006)).

Since the preparation of the IMPDs varies depending of the products to be submitted for approval, it will not be possible to define the detailed requirements applicable for all different product. Therefore, it only be discussed the requirements for submission a IMPD for a bioequivalence study (generic product versus non-modified comparator product authorized in ICH regions). This section was based in the guideline referred above.

Information on the chemical and pharmaceutical quality of authorised, non-modified comparator products in clinical trials

For comparator products to be used in clinical trials which have already been authorised in the EU/EEA, in one of the ICH-regions or one of the Mutual Recognition Agreement (MRA)-partner countries, it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA.

For products sourced from those countries outside the EU/EEA, information on the analytical methods needed for at least reduced testing (e.g. identity) should be provided. The relevant analyses, tests or checks necessary to confirm quality as required by Article 13 3(c) of directive 2001/20/EC shall therefore be based on proof of existence of the equivalent of a marketing authorisation, combined with confirmation of identity.

The applicant or sponsor of the clinical trial has to ensure that the IMP is stable at least for the anticipated duration of the clinical trial in which it will be used. For authorised products, it will be sufficient to state the respective expiry date assigned by the manufacturer.

Information on the chemical and pharmaceutical quality of investigational medicinal products containing existing active substances in bio-equivalence studies, e.g. generics (chemical substances)

This information is only applied for the test product.

5.2.1.S DRUG SUBSTANCE

Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate for the Quality of Medicines is acceptable.

5.2.1.S.1 General information: 5.2.1.S.1.1 Nomenclature

Information concerning the nomenclature of the drug substance (e.g. (proposed) INN-name, pharmacopoeial name, chemical name, code, other names, if any) should be given.

5.2.1.S.1.2 Structure

The structural formula should be presented.

5.2.1.S.1.3 General Properties

The main physicochemical and other relevant properties of the drug substance should be indicated.

5.2.1.S.2 Manufacture: 5.2.1.S.2.1 Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided.

5.2.1.S.2.2 Description of Manufacturing Process and Process Controls

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, a brief summary of the synthesis process, a flow chart of the successive steps including, for each step, the starting materials, intermediates, solvents, catalysts and reagents used should be provided. The stereo- chemical properties of starting materials should be discussed, where applicable.

5.2.1.S.3 Characterisation: 5.2.1.S.3.2 Impurities

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, impurities, possible degradation products and residual solvents deriving from the manufacturing process or starting materials relevant to the drug substance used for the bio-equivalence study should be stated.

5.2.1.S.4 Control of the Drug Substance: 5.2.1.S.4.1 Specifications

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvents and catalysts.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, specifications, tests used as well as the acceptance criteria should be provided for the batch(es) of the drug substance(s) intended for use in the bio-equivalence study.

5.2.1.S.4.2 Analytical Procedures

Not Applicable (assuming that DS comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP).

5.2.1.S.4.3 Validation of Analytical Procedures

Not Applicable (assuming that DS comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP).

5.2.1.S.4.4 Batch Analyses

Certificates of analyses or batch analysis data for the batch(es) intended for use in the planned bio- equivalence study or, in their absence, for representative batches, should be supplied. The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and test results should be listed.

5.2.1.S.4.5 Justification of Specifications

Not Applicable (assuming that DS comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP).

5.2.1.S.5 Reference Standards or Materials:

Not Applicable (assuming that DS comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP).

5.2.1.S.6 Container Closure System:

The immediate packaging material used for the drug substance should be stated.

5.2.1.S.7 Stability:

The available stability data should be provided in a tabulated form. Alternatively, confirmation that the active substance will meet specifications at time of use will be acceptable.

5.2.1.P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

5.2.1.P.1 Description and Composition:

The qualitative and quantitative composition of the IMP should be stated.

Practical Example:

Table 16 *- Composition of drug product*

Composition	%	mg/tablet
DS	0.08	0.10
Excipient A	30.00	36.00
Excipient B	29.08	34.90
Excipient C	38.00	45.60
Excipient D	1.67	2.00
Excipient E	0.17	0.20
Excipient F	1.00	1.20
TOTAL	**100.0**	**120.00**

5.2.1.P.2 Pharmaceutical Development:

A brief narrative description of the dosage form should be provided.

Practical Example:

The current IMPD refers to test product tablets (Code name: X), manufactured at Bluepharma – Indústria Farmacêutica, S.A., and is intended to support a Clinical Trial Application for a Bioequivalence (BE) study. The BE study favourable outcome is going to be used to support a Marketing Authorization Application (MAA) in USA for test product extended-release tablets.

The objective of the pharmaceutical development of test product extended-release tablets was to obtain a generic medicinal product of the US/FDA-approved reference medicinal product marketed in USA which was firstly approved in USA on September 2009.

Although the pharmaceutical development was carried-out under the EU GMP framework, it was oriented in accordance with the US/FDA requirements, namely in what concerns to the use of USP/NF referential for the drug product, drug substance and excipients, as well as, to the use of the recommendations on the drug product dissolution method and on the BE studies issued by "US/FDA – Office of Generic Drugs". As outlined in the EU Guideline "CHMP/QWP/185401/2004 - Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products

in Clinical Trials", for IMPs to be used in clinical trials, reference to either the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) is acceptable.

The pharmaceutical development purpose for test product project was to establish a suitable formulation and manufacturing process for test product extended-release tablets, the generic drug product of the reference medicinal product, marketed in USA.

The development encompassed the study of the physical-chemical characteristics of reference medicinal product, as well as the active principal ingredient DS.

The reference medicinal product is presented in the market as round tablets of 0.1mg strength.

The reference medicinal product´s qualitative formulation, which was used as a basis for pharmaceutical development of the generic drug, is depicted in the following table:

Table 17 *- Qualitative formulation of drug product*

Composition	Functional Category
DS	Drug substance
Excipient A	Filler
Excipient B	Binder
Excipient C	Matrix-forming agent
Excipient D	Surfactant
Excipient E	Glidant
Excipient F	Lubricant

During the pharmaceutical development and manufacturing process screening, several parameters were tested and the main conclusions are:

- Dry granulation, performed with a Roller Compaction process, was considered the most suitable process to achieve adequate pharmacotechnical properties of the powder mixture, adequate API homogeneity, similarity to the reference medicinal product and complete drug substance release under dissolution test;
- The final formulation contains qualitatively the same excipients as the reference medicinal product (with grades considered adequate;
- The critical quality attributes of the drug substance to be used on the test product extended-release tablets product were defined regarding particle size and grade;

- The pressure value of the roller unit, fine granulator screens, roller gap are considered as Critical Process Parameters to obtain the most suitable manufacturing process;
- The defined critical process parameters of compression process was compression force/ tablet hardness;
- Analytical tests showed that the obtained extended-release tablets are within the required specifications for assay, dissolution, uniformity of dosage unit, related substances, water content, residual solvents as well as good appearance;
- The choice of the primary packaging material was based on the characterization of the primary packaging materials of the Reference Product Material: HDPE bottles (40cc).

5.2.1.P.3 Manufacture: 5.2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided. In case multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities in the manufacturing chain should be clearly indicated.

5.2.1.P.3.2 Batch Formula

The batch formula for the batch to be used in the planned bio-equivalence study should be presented. Where relevant, an appropriate range of batch sizes may be given.

5.2.1.P.3.3 Description of Manufacturing Process and Process Controls

A flow chart of the successive steps, including the components used for each step and including any relevant in process controls, should be provided. In addition, a brief narrative description of the manufacturing process should be included.

5.2.1.P.3.4 Control of Critical Steps and Intermediates

If critical manufacturing steps have been identified; their control as well as possible intermediates should be documented.

Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

5.2.1.P.3.5 Process Validation and/or Evaluation

Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP and non-standard manufacturing processes.

5.2.1.P.4 Control of Excipients: 5.2.1.P.4.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food- chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided.

5.2.1.P.4.2 Analytical procedures

Not applicable (assuming reference to a pharmacopoeial monograph listed)

5.2.1.P.4.3 Validation of Analytical Procedures

Not applicable.

5.2.1.P.4.4 Justification of Specifications

Not applicable.

5.2.1.P.4.5 Excipients of Animal or Human Origin

Cf. Appendix 7.2.1.A.2.

5.2.1.P.4.6 Novel Excipients

For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be provided in annex 2.1.A.3 consistent with the respective clinical phase (c.f. section 7.2.1.A.3), details are to be included on e.g. their manufacturing process, characterisation and stability.

5.2.1.P.5 Control of the Investigational Medicinal Product:

5.2.1.P.5.1 Specifications

The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria.

5.2.1.P.5.2 Analytical Procedures

The analytical methods should be described for all tests included in the specification (e.g. dissolution test method).

For complex or innovative pharmaceutical forms, a higher level of detail may be required.

5.2.1.P.5.3 Validation of Analytical Procedures

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the validation results should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

5.2.1.P.5.4 Batch Analyses

Certificates of analysis or batch analysis data for the batch(es) intended to be used in the planned bio- equivalence study or, in their absence, representative batches, should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

Practical Example:

Table 18 *- Physicalchemical and analytical results of drug product*

	Test Product		
Batch	**X**		
Appearance	 White to off-white round, biconvex tablets with debossing: “V” on one side and “20” on the other side.		
Identification			
HPLC-RT	Complies		
HPLC-PDA	Complies		
Weight (mg)	**Beginning**	**Middle**	**End**
Min	119.6	119.7	120.0
Max.	122.4	122.0	122.3
Average	**121.2**	**120.8**	**121.0**
Diameter (mm)	**Beginning**	**Middle**	**End**
Min	6.18	6.35	6.36
Max.	6.27	6.42	6.45
Average	**6.20**	**6.39**	**6.41**
Thickness (mm)	**Beginning**	**Middle**	**End**
Min	3.71	3.75	3.76
Max.	3.84	3.82	3.82
Average	**3.79**	**3.79**	**3.79**
Hardness (N)	**Beginning**	**Middle**	**End**
Min	38	39	39
Max.	48	46	46
Average	**42**	**42**	**43**
Water content	**4.8%**		
Assay (%)	**99.5**		
UDU	**Complies (AV=4.7)**		
Average weight	**Complies (120.5mg)**		
Related Substances			
Impurity A	ND		
Impurity M	ND		
Single unknown impurity	**≤0.1%**		
Total Impurities	**≤0.1%**		
Dissolution			
2h	Complies at L1: **36%** (33.9 - 38.6%)		
4h	Complies at L1: **59%** (56.1 – 61.9%)		
8h	Complies at L1: **81%** (77.2 – 84.0%)		
18h	Complies at L1: **96%** (93.1 – 100.9%)		

- Dissolution Profile in HCl 0.01N + Phosphate Buffer pH 7.0 (HPLC) – OGD dissolution method

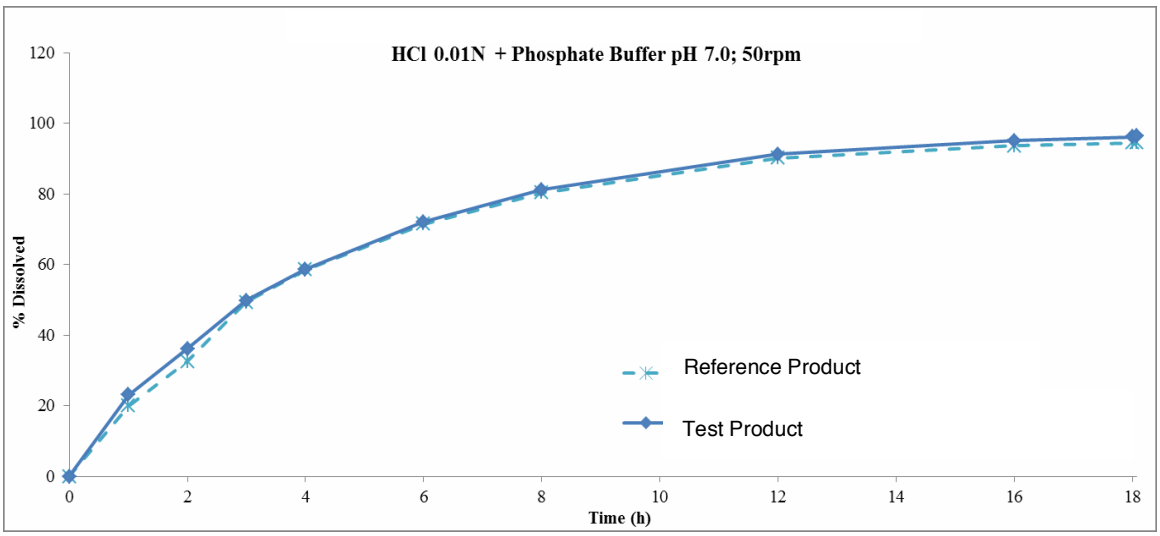

Figure 5 *- Dissolution Profie in OGD method of reference vs test product*

- Dissolution Profile in HCl 0.1N (HPLC)

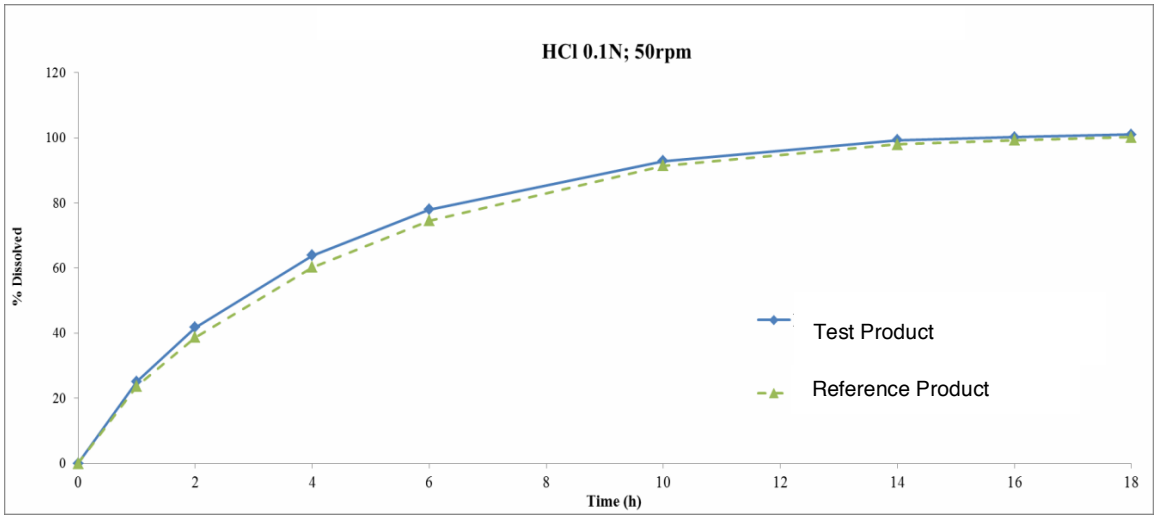

Figure 6 *- Dissolution Profile in HCl 0.1N of reference vs test product*

- Dissolution Profile in Acetate Buffer pH 4.5 (HPLC)

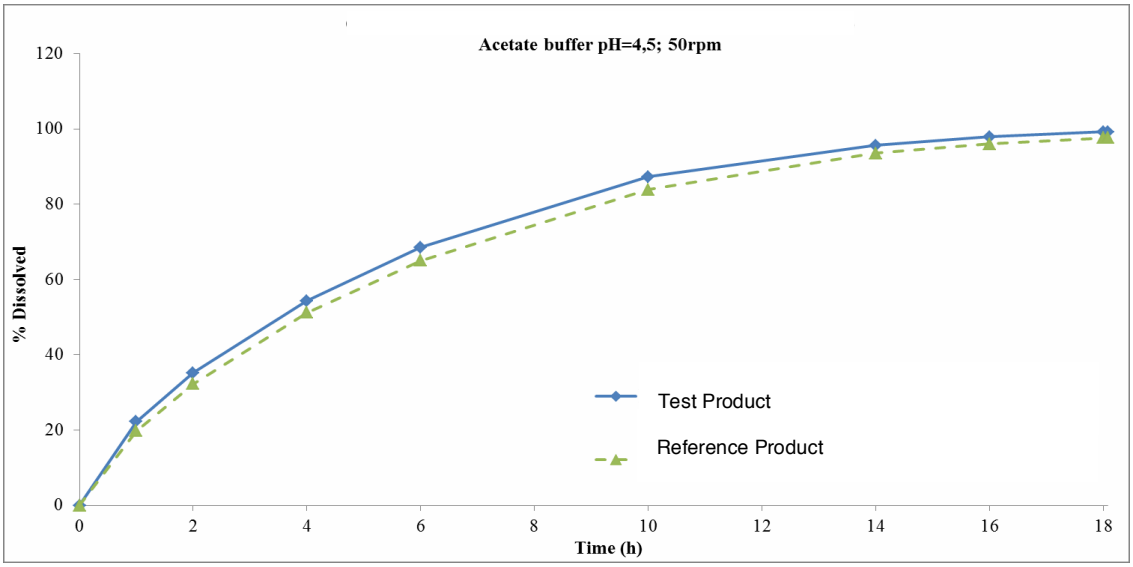

Figure 7 *- Dissolution Profile in Acetate buffer pH 4.5 of reference vs test product*

- Dissolution Profile in Phosphate Buffer pH 6.8 (HPLC)

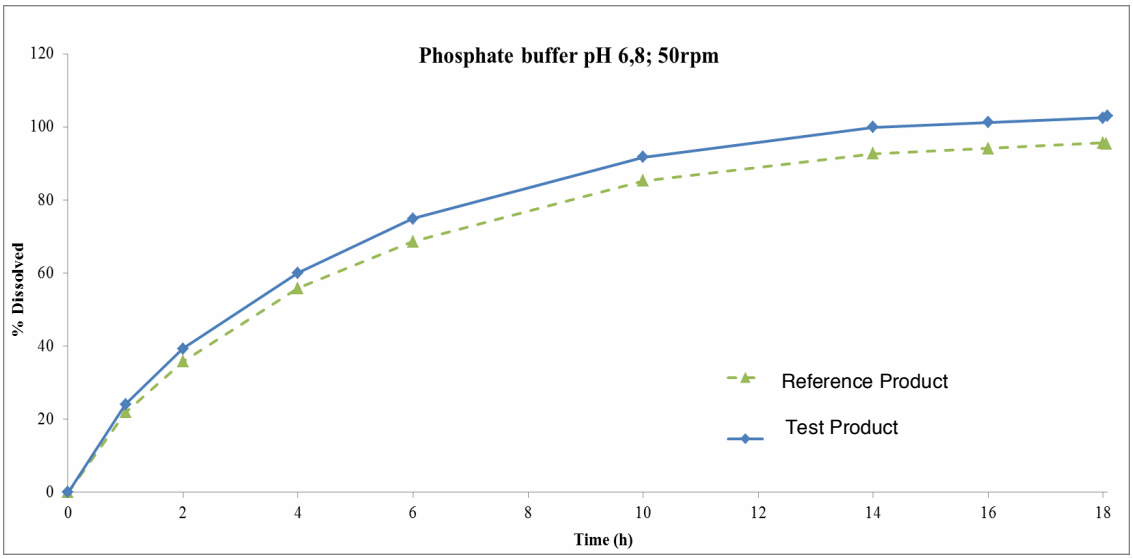

Figure 8 *- Dissolution Profie in Phosphate buffer pH 6.8 of reference vs test product*

After analysis of both Test Product Feasibility batch and RLD, it can be stated that:

- Regarding **Assay**, test product Feasibility batch has a similar result when compared with RLD 0.1mg ER (99.5 and 99.2%, respectively).
- In what concerns **UDU**, test product Feasibility batch complies with Specification.

- After analysis of **Related Substances** profile, it can be concluded that test product Feasibility batch has a lower impurities profile when compared with RLD 0.1mg ER, and the results are in accordance with Specification.
- Under HCl 0.01N + Phosphate Buffer pH 7.0 (**OGD medium**), the dissolution profile of Test Product Feasibility batch is very similar to RLD. Similarity factor f_2 value (**83.47**) confirms the *in vitro* similarity between the Feasibility batch and RLD is thus confirmed.
- Dissolution profiles in other media also revealed similar results between test product and RLD.

5.2.1.P.5.5 Characterisation of Impurities

Additional impurities/degradants observed in the IMP, but not covered by section 5.2.1.S.3.2, should be stated.

5.2.1.P.5.6 Justification of Specification(s)

It will be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the drug product. Toxicological justification should be given, where appropriate.

5.2.1.P.6 Reference Standards or Materials:

The parameters for characterisation of the reference standard should be submitted, if no compendial reference standard is available.

Section 5.2.1.S.5 - Reference Standards or Materials - may be referred to, where applicable.

5.2.1.P.7 Container Closure System:

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided. For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

Practical Example:

For marketing authorization application purposes, test product tablets are intended to be packaged in HDPE bottles with a silica canister containing 1g of silica gel. For the bioavailability/bioequivalence study concerned by the current IMPD, unitary doses, primary packaged in the bottles, are going to be individualized, per subject, using HDPE bottles as container closure system.

Available stability data presented in the following section proves that the product is stable in the concerned container closure systems.

5.2.1.P.8 Stability:

For bioequivalence studies, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under accelerated and long-term storage conditions will have been initiated. The results from at least one month accelerated studies or the results of the initial phase of studies under long-term storage conditions should be summarised in a tabulated form. Supporting data from development studies should also be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the bio-equivalence study should be provided. Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study.

Practical example:

Test Product tablets are packaged in HDPE bottles with a silica canister containing 1g of silica gel. For the bioavailability/bioequivalence study concerned by the current IMPD, unitary doses, primary packaged in the bottles, are going to be individualized, per subject, using HDPE bottles as container closure system.

During Galenical Development work performed, Test Product tablets formulation and manufacturing process were developed. Considering Test Product tablets, a laboratorial batch was produced (Trial #11B tablets - Batch: 000000000B) according to the final formulation. The purpose of this study was to verify how the quality of Test Product tablets varies in time under influence of temperature and humidity and to provide

evidence of its shelf-life and recommended storage conditions. Analyses were performed according to the defined analytical procedure.

Table 19 *- Stability results of drug product*

Drug product: X **Date of Storage:** 20/07/2016 **Storage condition:** 40ºC / 75% RH	**Batch no.:** 000000000B **Manufacturing date:** **Packing material:** HDPE bottles with a silica canister containing 1g of silica gel

Drug substance: X **Batch no.** 000000AB

Parameter	**Specification**	**Testing point (month) / results**	
		0	**1M**
Identification			
HPLC-RT	Must comply	Complies	Complies
HPLC-PDA		Complies	Complies
Assay	90.0 –	96.51	103.11
Related substances (HPLC)			
Impurity A	1.0%	ND	ND
Impurity B	1.0%	ND	ND
Single unknown impurity	NMT 1%	0.05	0.06
Total impurities	NMT 3%	0.13	0.18
Dissolution			
2h	25-45%	37.55	36.40
4h	50-70%	61.88	60.73
8h	70-90%	83.18	81.58
18h	NLT 80%	97.73	97.32
Average weight	Must	120.92	125.42

The stability of the Drug Product was accessed also for dissolution profile on Trial #11B analysed at T0 and T1M at accelerated conditions, in release medium.

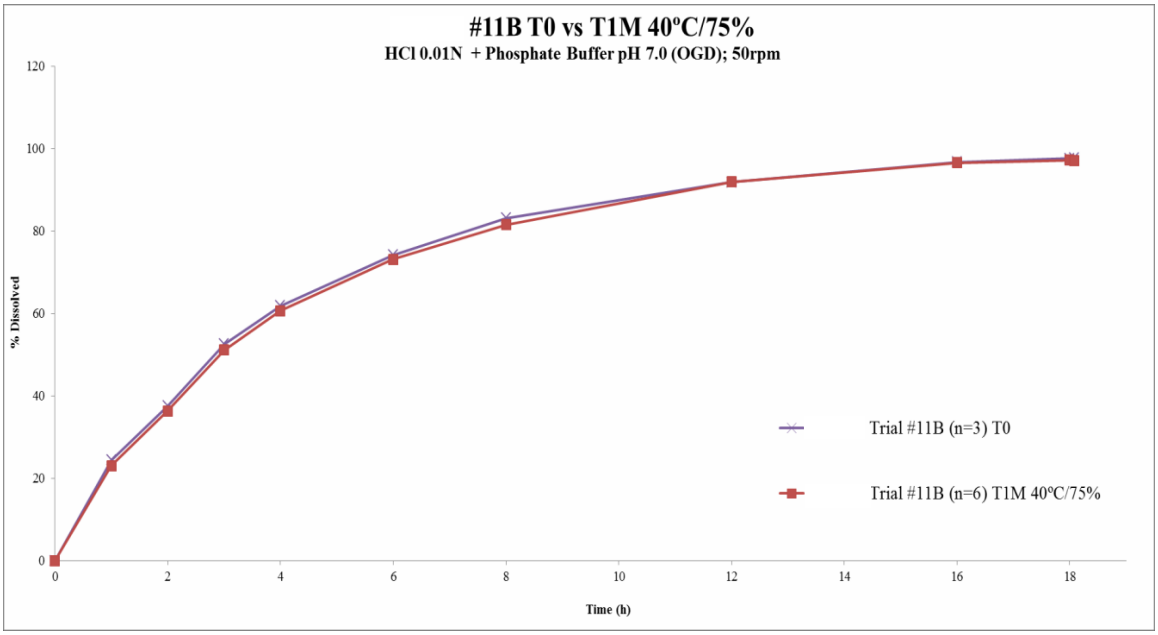

Figure 9 *- Dissolution profile of drug product T0 vs T1M*

Based on the available data for the laboratorial scale batch, after 1 month storage under 40ºC/75%RH accelerated conditions, the developed test product tablets complies with all tested critical parameters, namely assay, impurities and dissolution profile. All tested parameters comply with product specification.

Taking into consideration the presented stability data, it can be concluded that test product tablets is stable for at least 2 months in the above mentioned packaging material, stored at 25ºC/60%RH.

Considering that, based on the development data, the stability data of feasibility batch is expected to confirm the stability results of the laboratory scale batch (batch no. 000000000B).

To confirm the behaviour of the test medicinal product and its shelf life and respective recommended storage conditions, a stability program for a feasibility batch of Test Product tablets is packaged in HDPE bottles with a silica canister containing 1g of silica gel, encompassing test biobatch no. LP000000. This stability test was initiated under ICH long-term and accelerated storage conditions.

Additionally, the applicant establishes the commitment to administer to each subject finished product compliant with approved specifications provided in section 2.1.P.5.1.

Stability of the clinical batch

At this early stage of development, expiration / re-test date of the clinical batch (biobatch) will be set on the generated stability data of the stability program at a laboratorial-scale. At the time of this submission, 1 month of compliant stability data generated with a laboratory scale batch at accelerated condition are available (batch no. 0000000000B). Taking into consideration the available stability data, test product (biobatch: LP000000) can be labelled with an expiry date of at least 2 months after production.

Post-approval Stability Protocol and Stability Commitment

Preliminary stability study was designed to be performed for 6 months in long-term conditions (25ºC ± 2ºC/60% RH ± 5 %) and 3 months at accelerated conditions (40ºC ± 2ºC/75% RH ± 5 % RH).

The applicant commits to yield stability data at accelerated and long term storage conditions for test product tablets (biobatch no. LP000000) in HDPE bottles with a silica canister containing 1g of silica gel.

IMPs Expedition

After Clinical trial authorization by the regulatory entity, the manufacturer ships the IMPs to the CRO. Since the documentation which should go with the IMPs depends to the country where the clinical trial will take place, I will only address the documentation needed to ship the IMPs from a Portuguese company to a Portuguese CRO. Therefore, the documents which should follow the investigational products are:

- Certificate of Analysis of the test product biobatch;
- Results of Analysis of the RLD biobatch;
- Certificate of Compliance (Qualified Person states that the test product batch had been manufactured under GMP conditions);
- BSE/TSE declaration (quality management states that the formulation of test product batch does not contain any ingredient of animal origin nor come in contact with animal products during storage or transportation);
- Proforma Invoice (stating that the shipped products don´t have commercial value).

5. Conclusion

During the elaboration of this thesis several key points of pharmaceutical development where considered. This combination of methodologies and techniques allow for a global control of a complex multi-stage development. A tight control of the entire process allows for an expedite optimized development.

The creation of a multidisciplinary team that evaluates all project from their initial stages, allows for an intrinsic knowledge of the questions in hand and their difficulties. With the cooperation of multiple departments problems can be addressed more efficiently reducing delays and failures in the internal communication.

This organisation has an approach to development based on an empirical and systematic processes. By combining both strategies, a general view of the project can be achieved as well as in later stages of the project a more precise and methodical quality by design approach allows to optimize processes and improve the quality of the final product. By using quality by design it is possible to understand the limits of the processes and adjust the variables without affecting the quality of the final product.

The galenical development has a fundamental role in the compilation of the data submitted by regulatory affairs for clinical trials. The close contact between the needs of the regulatory affair and the data supplied by galenical development are fundamental for a higher approval rate from the regulatory entities.

Even though the pharmaceutical industry is one of the most competitive environments, the creation of unrealistic timelines, generally contributes for the unsatisfaction of the intervenients as well as the clients. Maintaining a balance between time spent on a problem and assuming the end point of the development has been achieved is crucial for obtaining the best results. Tight timelines are a necessary evil that allow for a cost efficient development but it is normal that such tight schedules have a direct impact on the final quality of the product. The creation of a buffer zone during development would allow for a higher certainty during development decreasing the chances of failure in later stages of the process. This higher investment on the earlier stages of the development have a significant lower costs than a failure at later stages of the process, such as during production of pilot batches and clinical trials.

In the same way that a better planning can have a significant impact in realistic timelines, the improvement of internal and external communication impacts also in customer´s satisfaction and staff´s motivation. However, the continuous improvement of internal and

external communication does not mean that the number nor the time of meetings between the intervenients of the projects should increase. In fact, through my point of view the large number of meetings can be very often time consuming without productive results, leading in that way to a lack of efficiency. Well planned meetings during a short period of time with key persons can be effective and can improve the understanding of the project status.

Currently Bluepharma evaluates the dissolution profile of the drug products which allows to understand the solubility of the API on physiological pHs. However, other type of studies, like permeability studies are essential to understand the behaviour of the drug substance in-vivo. With this new technique errors during the clinical trial stages could be prevented resulting in a more improved product without the necessity of re-run bioequivalence studies.

As the pharmaceutical industry is constantly innovating techniques, processes and materials, the staff training is essential for the success of the teams. The technical improvement of each collaborator on a specific subject allows have a very specialized team in a wide range of subjects instead of a team with a wide range of basic knowledge, contributing for the professional improvement of the collaborators results in more accomplished, efficient and valued team.

In summary, the points that I consider that could culminate in an improvement for the existing system are: define realistic timelines, have better and more efficient planning and improve the internal and external communication. The need of study other type of *in-vitro* tests which can help to predict the results of bioequivalence studies and give to the staff more and better training are other critical points that in my opinion should be optimised.

In conclusion, a deeper analysis could be performed for the process of pharmaceutical development by conducting an optimization study of existing strategies and possible improvements.

References

- A. Fahr, X. L. (2007). Drug delivery strategies for poorly water-soluble drugs. *Expert Opin Drug Deliv* , pp. pp. 403–416 .
- Basu, P. (2010). *Improving Pharmaceutical Product Development and Manufacturing: Impact on cost of drug development and Cost of Goods Sold for pharmaceuticals.* Berlin: World Drug Manufacturing Summit.
- *Bluepharma Site*. (n.d.). Retrieved 2016, from https://www.bluepharma.pt/about.php
- Brown, S. a. (1995). Product development: past research, present findings, and future directions. *Academy of management review* , pp. pp.343–378.
- *European Investigational Medicinal Product Dossiers*. (n.d.). Retrieved from http://www.imp-dossier.eu/imdp_guidance/
- FDA, U.S. (2004). Guidance for Industry: Changes to an Approved NDA or ANDA.
- G.L. Amidon, H. L. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability . pp. pp. 413–420 .
- Gerwin, D. a. (2002). n Evaluation of Research on Integrated Product Development. *Management Science* , pp. pp.938–953.
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. (2006). *committee for medicinal products for human use (CHMP).*
- H. Leuenberger, M. L. (2005). Pharmaceutical powder technology-from art to science: the challenge of the FDA's process analytical technology initiative . *Adv Powder Technol* , pp. pp. 3–25 .
- ICH Q10. (2008). PHARMACEUTICAL QUALITY SYSTEM Q10.
- ICH Q8(R2). (August 2009). PHARMACEUTICAL DEVELOPMENT Q8(R2).
- ICH Q9. (2008). *PHARMACEUTICAL QUALITY SYSTEM.*
- J.B. Dressman, M. V. (2007). Estimating drug solubility in the gastrointestinal tract . *Adv Drug Deliv Rev* , pp. pp. 591–602 .

- Koufteros, X. V. (2005). nternal and External Integration for Product Development: The Contingency Effects of Uncertainty, Equivocality, and Platform Strategy. *Decision Sciences* , pp. pp.97–133.
- L.X. Yu, G. A. (2002). Biopharmaceutics classification system: the scientific basis for biowaiver extensions . *Pharm Res* , pp. pp. 921–925 .
- McDonough, E. (2000). Investigation of Factors Contributing to the Success of Cross-Functional Teams. *ournal of Product Innovation Management* , pp. pp.221–235.
- *Particle sciences*. (n.d.). Retrieved 2016, from http://www.particlesciences.com/news/technical-briefs/2011/biopharmaceutical-classification-system.html
- R.N. Davé, E. B. (2013). Special issue on pharmaceutical powders: towards developing understanding of the influence of materials and processes on product performance . *Powder Technol* , pp. pp. 1–4 .
- S. Onoue, Y. K. (2012). Physicochemical and pharmacokinetic characterization of amorphous solid dispersion of tranilast with enhanced solubility in gastric fluid and improved oral bioavailability . *Drug Metab Pharmacokinet* , pp. pp. 379–387
- *Science direct*. (2016). Retrieved from http://www.sciencedirect.com/science/article/pii/S1818087614000348
- Y. Kawabata, K. W. (2011). Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. *Int J Pharm* , pp. pp. 1–10 .
- Ziegler, R. M. (2014). *Managing Integrated Development in the Pharmaceutical Industry: A Cross-Functional Approach to Development of More Efficient Manufacturing Processes.* Dissertation of the University of St. Gallen, School of Management, Economics, Law, Social Sciences and International Affairs.